"Development of Transition Metal Free Mild Oxidative Methods for Application in Organic Synthesis"

Summary of Work (5000 Words)

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Chapter I

Visible-Light Mediated Oxidative Desulfurization-Oxygenation in Cyclic Thio-Amide

Introduction:

Owing to the high efficiency found in the natural photosynthetic reaction centers (e.g., chlorophyll), visible-light mediated photo-redox catalysis has emerged as a conceptually new and viable alternate to conventional harsh reaction conditions and eludes the practice of stoichiometric redox reagents.[1,2] In this regard, visible light photo-catalytic reactions are innately advantageous, since activation occurs by light as the greenest energy source.[3] Light-mediated processes can generate various reactive intermediates that cannot be frequently obtained using conventional thermal strategies.[4] In this context it must be mentioned that organic photocatalysts are particularly attractive because of their nontoxicity, cheapness, strong absorption of visible light, more synthetic versatility, and finer tuning of the redox properties.[5] Therefore, it is not surprising that recently organic photocatalysts have engrossed immense interest and boasted a diversity of studies on organic molecule activation.

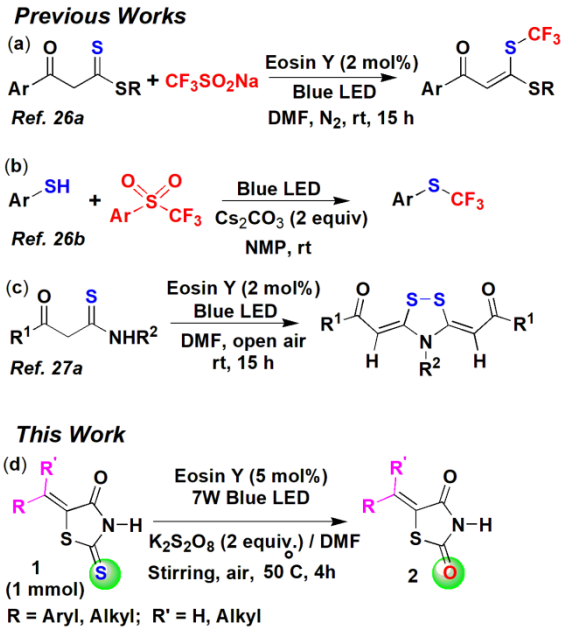
Again, selective transformation of thioamide to amide under extremely mild conditions, so that other functional moieties are not affected, represents a powerful tool to afford various biologically relevant molecules. For example, purine and pyrimidine bases are integral part of DNAs, RNAs, vitamins such as riboflavin, alkaloids, and numerous drug molecules.[6] They are very often constructed from thiourea instead of urea in order to harness the greater reactivity of thiourea and in the later stage the C=S is converted to C=O by various reagents. Moreover, this particular functional group manipulation is very frequently required during the multistep syntheses of complex biologically important molecules which may contain many different sensitive functional groups. Furthermore, this reaction can be used as a convenient technique to introduce ^{18}O isotope in the carbonyl groups.[7] Therefore, a very efficient and mild condition for this transformation is very much essential. Until now several methods have been reported for thioamide to amide transformation using different reagents like $H_2O_2/SOCl_2$, $H_2O_2/TiCl_4$, ICl/aq. HCl, ^tBuOCl, Ar_2SeO, Ar_2TeO, N-nitrosamine species, $(CF_3CO)_2O$, MnO_2, bismuth(III) nitrate, H_2SO_5 supported on a silica, $H_2O_2/ZrCl_4$, $PdCl_2/CuCl/O_2$ etc.[7,8] However, development of milder and more sustainable methods are always desirable. Moreover, thioamide to amide conversion in cyclic systems is much less studied compared to their acyclic analogue. Therefore, our goal was to carry out the oxidative desulfurization-oxygenation in cyclic thioamide system in a very mild way and for that purpose we chose 5-arylmethylidene rhodanine as the model substrate. Conversion of thioxo to oxo group in rhodanine derivatives generates thiazolidine-2,4-diones (TZDs) which serve as the core structural components of various commercially available drugs such as rosiglitazone, troglitazone, and pioglitazone.[9,10] Until now only a very few reports are available depicting the thioamide to amide conversion in rhodanine derivatives using aqueous $ClCH_2COOH$,[11a] hydrogen peroxide,[11b] $Br_2/AcOH$,[11c] diacetoxyiodobenzene (DIB)[9a] and dibromoformaldoxime/$KHCO_3$.[10] However, the conversion of thioxo group in rhodanine derivatives into the corresponding oxygen analogue has never been comprehended photo-catalytically failing to harness the abundance of greenest energy source; light. Recently, Yadav et al. developed a light mediated eco-friendly approach for the conversion of thioamide to amide in acyclic system. Though the reaction was quite successful in acyclic system,

however the same approach failed to yield the product in our cyclic thioamide system. Therefore, we herein report a general and mild Eosin Y (EY) catalyzed visible light mediated oxidative desulfurization-oxygenation in cyclic system taking 5-arylmethylidene rhodanine as the model substrate using $K_2S_2O_8$ as an oxidant.

Again prudent choice of the terminal oxidant is critical in organic synthesis, since it determines the efficiency as well as greenness of the process. Many oxidants have found their application in oxidative organic transformations like molecular oxygen, DDQ, p-benzoquinone, TBHP, $PhI(OAc)_2$, I_2, metal oxidants, oxone, DTBP etc.[12] Among them potassium persulfate ($K_2S_2O_8$) received particular preference in academia and industries because of its cheapness, easy handling as it is odourless non-hygroscopic solid, solubility in aqueous as well as in many organic solvents, and strong oxidizing nature.[13] Furthermore, organic oxidative transformations involving $K_2S_2O_8$ do not leave any hazardous and corrosive waste to discard after the reaction, fostering the practices of green chemistry. Generally in absence of any external stimulus the oxidation by $K_2S_2O_8$ is considered to be a slow process. However, it is easily activated to produce sulfate radical anion ($SO_4^{\bullet-}$) by homolytic cleavage of peroxide linkage in presence light, heat or transition metal ions under mild conditions.[14] Steric repulsion between the two tetrahedral SO_4^- units makes the peroxide (O-O) linkage weak and becomes weaker in presence of heat, light etc. to give $SO_4^{\bullet-}$. This sulfate radical anion is the key to rate enhancement of photocatalytic oxidative reactions by $K_2S_2O_8$. Moreover, it is pertinent to mention that sulfate radical anion have a very high positive redox potential of 2.5−3.1 V, making it one of the strongest one electron oxidants.[14] Again it is pertinent to mention that this $SO_4^{\bullet-}$ generates other secondary oxidants such as singlet oxygen ($^1O_2$), hydroxyl radicals ($HO^{\bullet}$), superoxide radicals ($O_2^{\bullet-}$) which are engaged in different steps of the reaction and thus promote the oxidation of organic molecules. Since the discovery of Minisci reaction,[15a-b] Elbs persulfate[15c] and Boyland–Sims oxidations;[15c] $K_2S_2O_8$ continued to show its prominence in metal catalysed oxidative transformations and also as an alternative for many conventional transition metal catalyzed reactions.[14a] The type of oxidative transformation leveraging potassium persulfate includes trifuloromethylation,[16] alkylation,[17] arylation,[18] acylation,[19] nitration,[20] thiolation,[21] oxygenation,[22] thiocyanation,[23] phosphorylation[24] and many others.[16,25] However, despite all these success light mediated photocatalytic reaction involving $K_2S_2O_8$ as an oxidant has tremendous scope to explore by chemists.

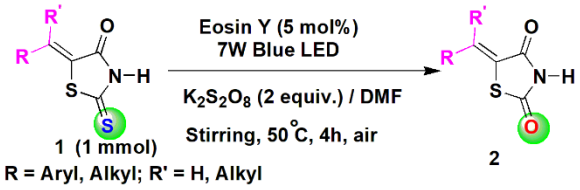
Results and Discussion:

Recently, visible light mediated photocatalytic transformations of thiols and thiocarbonyls to the corresponding S-trifluoromethyl groups (-SCF_3) have been achieved quite successfully using using Langlois' reagent (CF_3SO_2Na, sodium triflinate) or other –CF_3 transferring reagents as shown in **(Scheme 1a-b)**.[26] Again the photocatalytic oxidation of thiols leading to disulfide is quite established in literature.[27] For example, Sinha et al. recently reported elegant synthesis of 1,2,4-dithiazolidines from β-ketothioamides which proceeded via a light-assisted photocatalytic oxidative S-S bond formation as the key step **(Scheme 1c)**.[27a] However, notably our attempt to carry out S-trifluoromethylation of 5-arylalkylidene-rhodanine (**1**) did not afford 5-arylalkylidene-2-trifluoromethylsulfanyl-thiazol-4-one following similar method. Neither had we got the corresponding disulfide product.



Scheme 1. Comparison of our work with related previous works.

More interestingly here we isolated a new product however, in trace amount. From the NMR and mass spectroscopic analyses we realized that the structure derived from thioxo to oxo conversion in 5-arylalkylidene-rhodanine (**1**) to give 5-arylalkylidene-thiazolidine-2,4-dione (**2**). This observation directed to an exploration in which we uncovered a general eosin Y catalyzed oxidative desulfurization-oxygenation of 5-arylalkylidene-rhodanine (**1**) compounds harnessing the environment friendly aspects of visible light. Moreover, $K_2S_2O_8$ could be used successfully as a mild and green terminal oxidant to afford the desired transformation **(Scheme 2)**. The synthesized compounds were characterized by ^{1}H, ^{13}C NMR and HRMS spectroscopic analyses. Here we realized that the obtained thiazolidine-2,4-dione (**2**) compounds are very crucial molecules owing to their great biological importance and therefore, interested to optimize the reaction conditions to increase the yield of the trace amount of the obtained 5-arylalkylidene-thiazolidine-2,4-dione (**2**). In order to do that, we undertook a lot of background studies and the results are summarized in **Table 1**. For the purpose 5-benzylidene-2-thioxo-thiazolidin-4-one (**1g**) which was obtained by Knoevenagel condensation between rhodanine and benzaldehyde was chosen as a model substrate to afford **2g**.



Scheme 2. General procedure for the conversion of thioamide to amide in rhodanine derivatives.

Table 1. Optimization of the reaction conditions.[a]

Sl. No.	Cat.	Oxidant	Sol.	Aerial Atmp.	Temp.	Light	Yield[b]
1	-	-	DMF	air	RT	-	-
2	EY	-	DMF	air	50	Blue	trace
3	EY	-	DMF	N_2	50	Blue	trace
4	EY	$PhI(OAc)_2$	DMF	air	50	Blue	30
5	EY	I_2	DMF	air	50	Blue	trace
6	EY	^tBuOOH	DMF	air	50	Blue	50
7	EY	$K_2S_2O_8$	DMF	air	50	Blue	92
8	EY	$K_2S_2O_8$	DMF	N_2	50	Blue	30
9	EY	$K_2S_2O_8$	DMF	O_2	50	Blue	32
10	EY	$K_2S_2O_8$	DMF	air	RT	Blue	40
11	EY	$K_2S_2O_8$	EtOH	air	50	Blue	80
12	EY	$K_2S_2O_8$	H_2O	air	50	Blue	trace
13	EY	$K_2S_2O_8$	EtOH /H_2O (1:1 v/v)	air	50	Blue	50
14	EY	$K_2S_2O_8$	EtOH	air	RT	Blue	52
15	EY	$K_2S_2O_8$	DCM	air	50	Blue	25
16	EY	$K_2S_2O_8$	Toluene	air	50	Blue	30

[a] Reaction condition: 5-Arylalkylidene-rhodanine (1) (1 mmol), photocatalyst (0.05 mmol), oxidant (2 mmol), 7W blue/green LED lamp, 4 hours stirring at different temperatures. [b] Isolated yields.

For the initial studies DMF was chosen a trial solvent because of good solubility of the highly polar substrates. The starting material did not respond at all in absence of oxidant, photocatalyst and light **(entry 1)**. However, in presence of Eosin Y as photocatalyst under blue light without any oxidant, only trace amount of the product was obtained both in air and also under inert atmosphere **(entries 2-3)**. This demonstrates the necessity of a stoichiometric oxidant in this reaction. Among the various oxidants used **(entry entries 4-7)**, $K_2S_2O_8$ came out as the preferred choice of oxidant due to the high yields **(entry 7)** of the product and low cost of $K_2S_2O_8$. Interestingly the reaction did not go well when performed under nitrogen atmosphere **(entry 8)**. Here, we initially thought that aerial oxygen played a role in this conversion along with $K_2S_2O_8$. However, when the reaction was carried out with only oxygen in closed condition, again very little conversion was observed **(entry 9)**. We came to the conclusion that water molecule is necessary for this transformation which is coming from the environmental moisture. However, the reaction did not go well in water as solvent, probably due to insolubility of the starting materials in aqueous medium. Again the reaction was unsatisfactory in solvents like DCM and toluene due to less solubility of the starting materials in these solvents. We varied the photocatalysts like fluorescein, rhodamine B, methylene blue and also light sources from blue to green. However, we get best result with Eosin Y under blue light irradiation in open air using 2 equivalents of $K_2S_2O_8$ as oxidant in DMF as solvent **(entry 7)**.

Once the optimized condition was obtained, in order to delineate the reproducibility of this protocol a number of 5-arylalkylidene-rhodanine (**1**) compounds were synthesized by Knoevenagel condensation between rhodanine and aldehydes and were employed for the said transformation. Aldehydes with

electron donating and withdrawing groups at o-/m-/p- positions, hetero-aromatic aldehyde, and aliphatic aldehyde were successfully employed affording good yields of the products. The substrate scope of this reaction is demonstrated in **figure 1**.

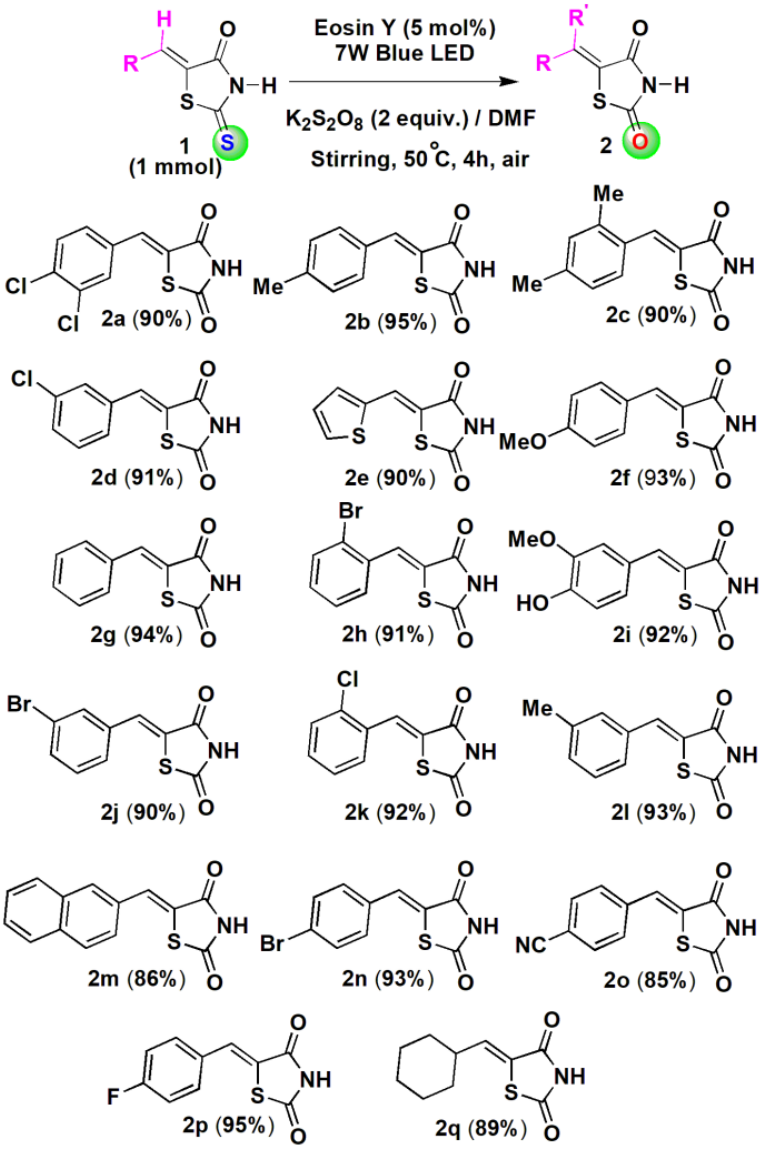


Figure 1. Synthesized thiazolidine-2,4-diones (**2**) obtained from the Knoevenagel condensation products (**1**) between rhodanine and aldehydes.

We further tried to extend the generality and broadness of this protocol and therefore, we have synthesized Knoevenagel condensation products (**3**) of different ketones and rhodanine and employed them for the above mentioned thioxo to oxo transformation. The substrate scope for this is shown in **figure 2**. In all cases the reaction occurred smoothly affording very good yields of the products.

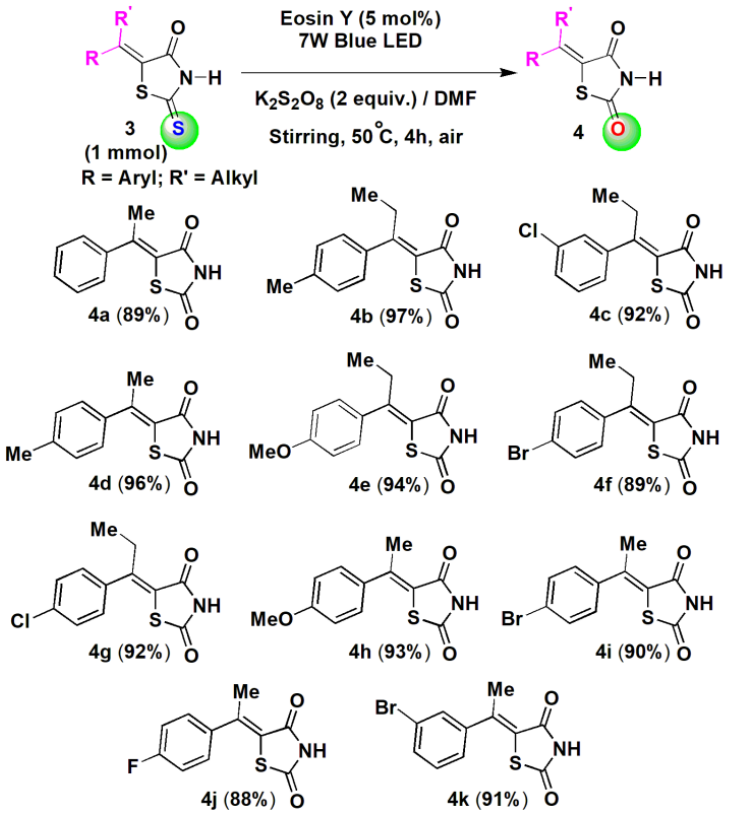


Figure 2. Synthesized thiazolidine-2,4-diones (**4**) obtained from the Knoevenagel condensation products (**3**) between rhodanine and ketones.

After both aldehyde and ketone, the scope of the reaction was further extended by carrying out the reaction on the Knoevenagel condensation products (**5**) of isatin derivatives and rhodanine to give the corresponding oxo-products (**6**) quite smoothly **(Figure 3)**.

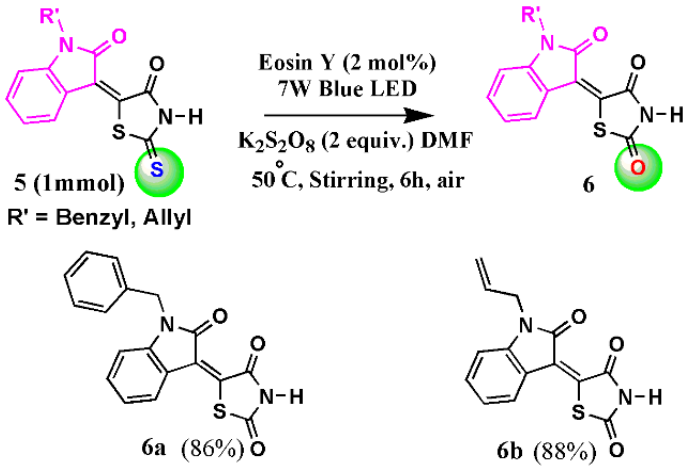


Figure 3. Synthesized thiazolidine-2,4-diones (**6**) obtained from the Knoevenagel condensation products (**5**) between rhodanine and isatin derivatives.

Interestingly the reaction was not successful when we took only rhodanine as substrate instead of 5-arylalkylidene-rhodanine. Here, it is presumed that this double bond at 5-position forms some electronic communication with the ring altering its redox potential. In bare rhodanine, the carbonyl (C=O) group at 4-position can undergo resonance only with the amide nitrogen making the nitrogen positively charged

as shown in **Figure 4**. This makes the thiocarbonyl group at C-2 position extremely electron deficient and thus difficult to oxidize. However, in 5-alkylidene rhodanine the olefinic bond at C-5 can also participate in resonance with the carbonyl group leaving the nitrogen neutral. Since, this particular structure should have contribution in overall resonance structure of the molecule, the C=S at C-2 is comparatively more electron rich and easily oxidizable.

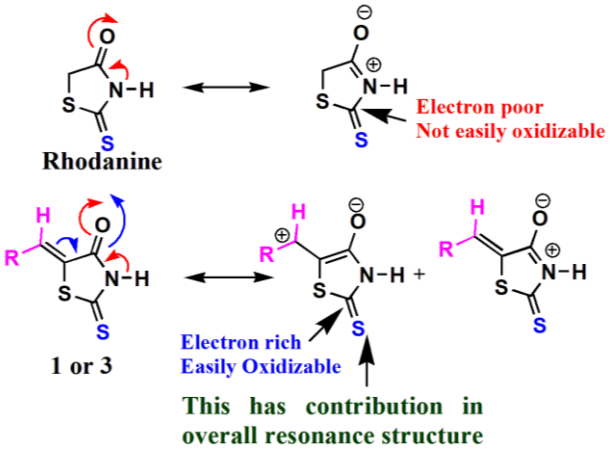
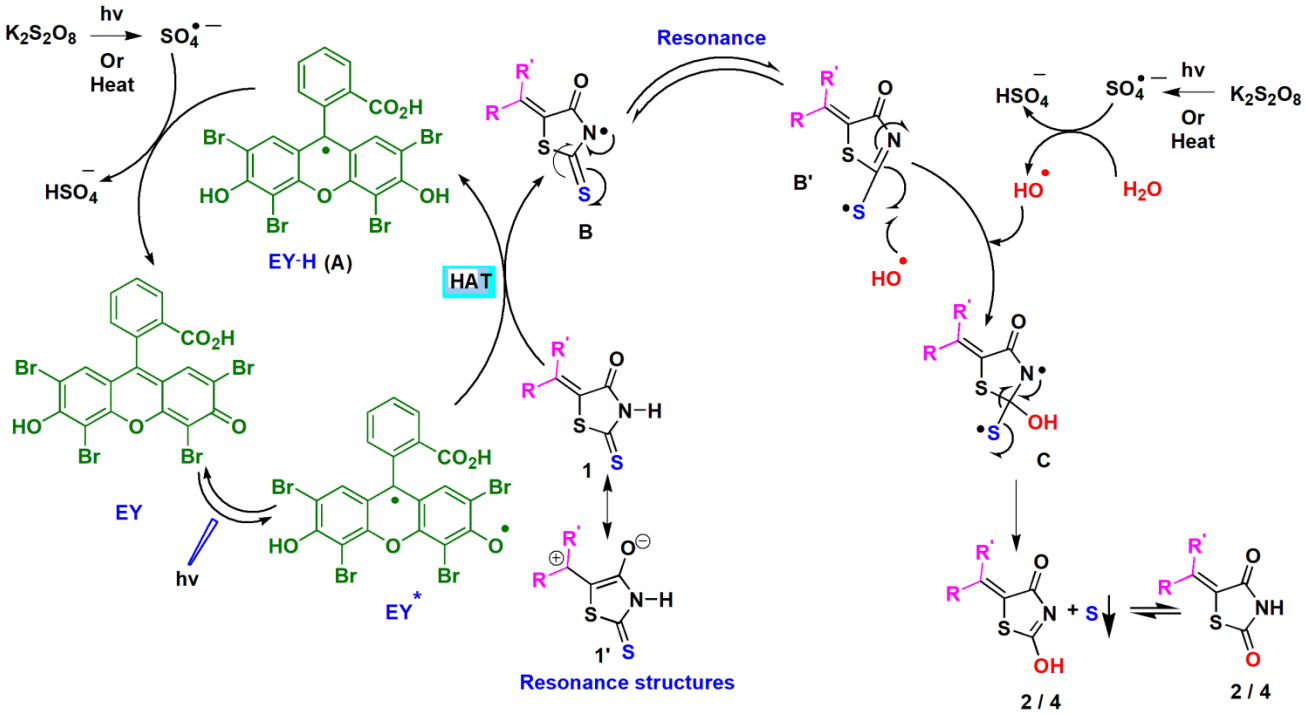


Figure 4. Structures to explain the inertness of rhodanine in comparison to 5-arylalkylidene-rhodanine in this reaction.

Now, based on the results obtained from different control experiments as mentioned earlier and literature studies[26b,27a] we herein propose the following reaction mechanism **(Scheme 3)**. As discussed earlier, the light or heat promoted decomposition of $K_2S_2O_8$ generates a sulfate radical anion ($SO_4^{\bullet -}$)[14] and at the same time the photocatalyst Eosin Y (EY) is activated to give excited state eosin (EY*).



Scheme 3. Plausible mechanistic pathway for the photocatalytic formation of **2** (or **4**).

The excited state eosin Y abstract hydrogen from 5-arylalkylidene-rhodanine (**1**), producing the radical intermediates **A** and **B** from eosin and substrate **1** respectively. The intermediate **A** undergoes oxidation by $SO_4^{\cdot -}$ to regenerate the ground state Eosin Y. Again, during optimization of the reaction condition it is established that two equivalents of $K_2S_2O_8$ are required and also water was essential for this reaction. Here the second equivalent of $K_2S_2O_8$ produces another sulfate radical anion which in turn accepts a hydrogen radical ($H^{\cdot}$) from water to produce the hydroxyl radical ($OH^{\cdot}$). Now, the intermediate **B** remains in equilibrium with another resonating structure **B′**. Next, **B′** undergoes hemolytic cleavage of the C=N bond and subsequently combines with the hydroxyl radical ($OH^{\cdot}$) through C-2 carbon atom to form intermediate **C**. Finally elimination of elemental sulphur affords the final product **(2 or 4)**.

Lastly, in order to validate the applicability of this protocol in other cyclic thioamide systems, we carried out the reaction on 3,4-dihydropyrimidine-2(1H)-(thio)ones. Importantly, the thioamide to amide transformation went very well to afford the corresponding the oxygen analogue in good yields **(Figure 5)**.

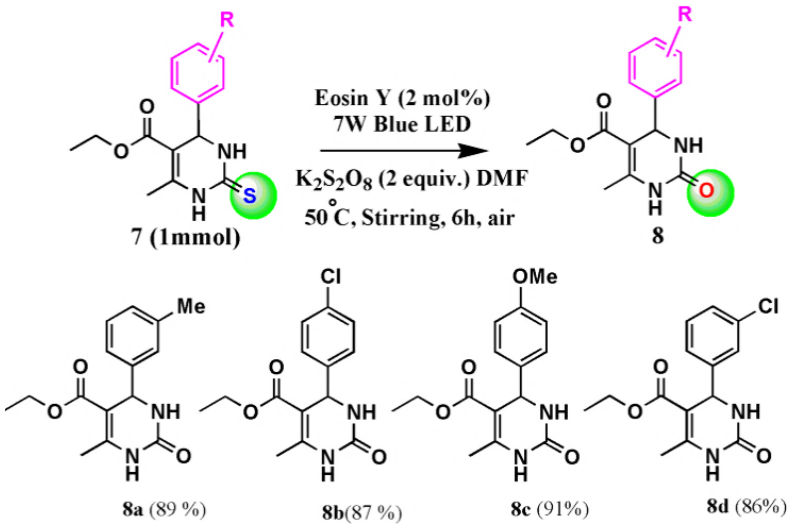
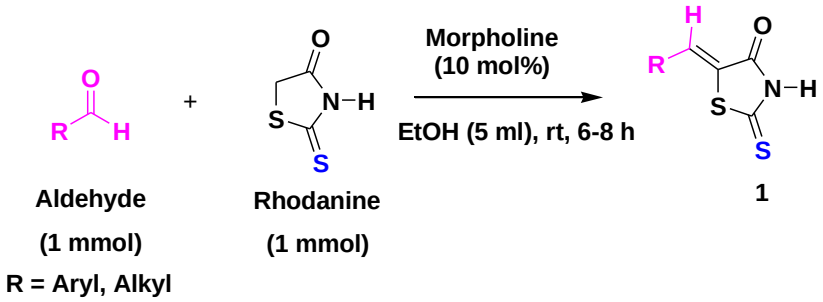


Figure 5. Synthesized 3,4-dihydropyrimidine-2(1H)-ones (**8**) from corresponding thio-analogue.

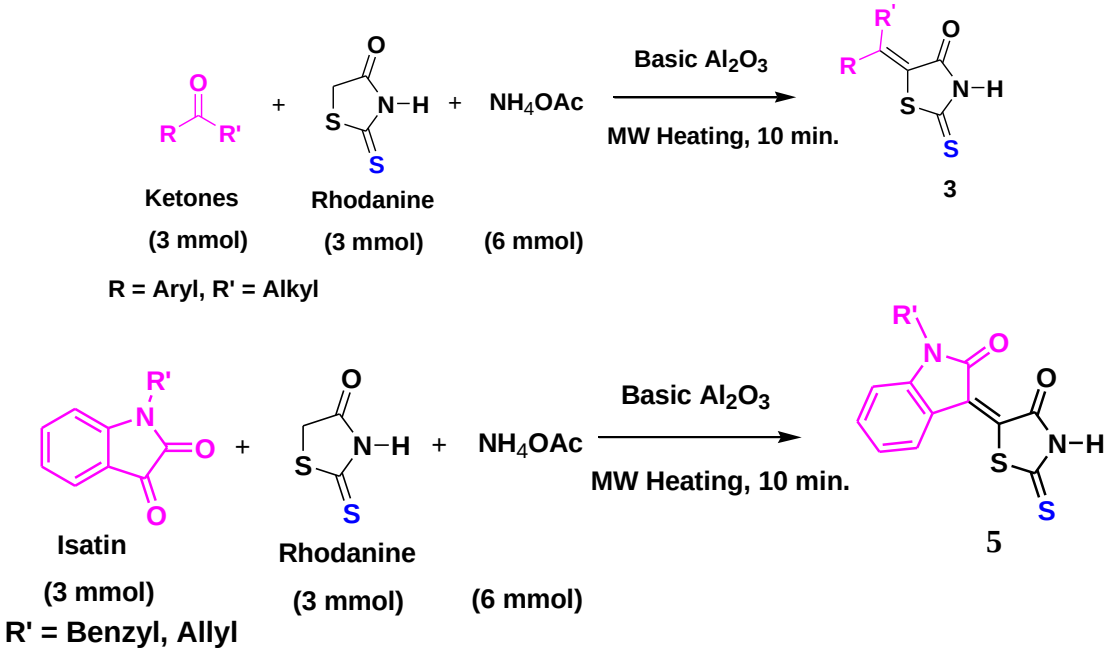
Experimental Section:

Preparation of starting material 1 (Knoevenagel condensation product of rhodanine and aldehydes):



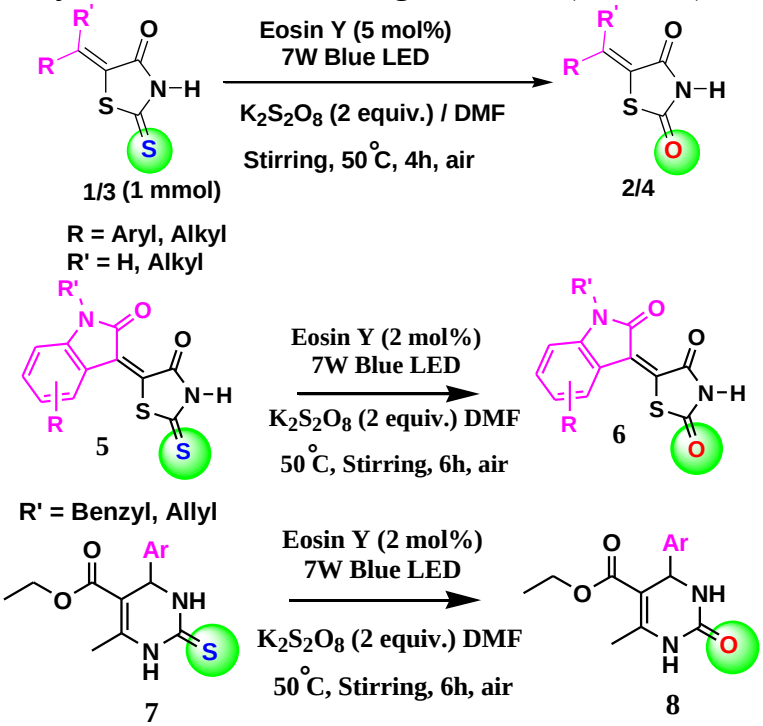
Rhodanine (1 mmol), different aldehydes (1 mmol), and catalytic amount of morpholine (0.10 mmol) in 5 ml EtOH were taken in a 50.0 mL round bottom flask and stirred on a magnetic stirrer at room temperature for 6-8 hours. After completion of the reaction as confirmed by TLC, the solid product was filtered and washed with little ethanol. Then the crude product was further purified by recrystallization from ethanol.

Preparation of starting material 3 (or 5) (Knoevenagel condensation product of rhodanine and either ketones or or N-substituted isatins):



The synthesis was done following the literature procedure with appropriate modifications.[1] Rhodanine (3 mmol), ketones (or N-substituted isatins) (3 mmol), ammonium acetate (6 mmol), and basic alumina (3g) and were mixed thoroughly in a mortar. The reaction mixture was taken in a 50 ml conical flask and heated under microwave irradiation. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. The reaction mixture was extracted into dichloromethane then filtered to separate the alumina. The solvent was removed under reduced pressure by rotatory evaporator and purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

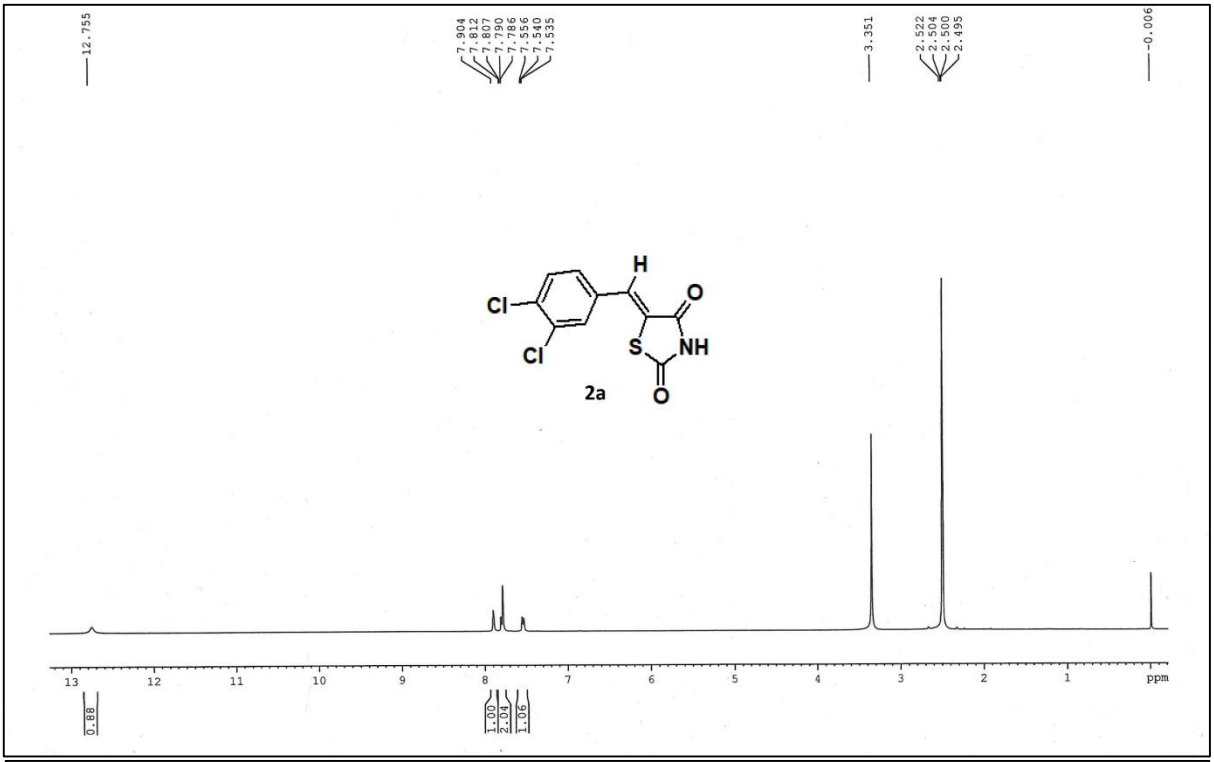
Procedure for photocatalytic conversion of starting material 1 (or 3, 5, 7) to 2 (or 4, 6, 8):

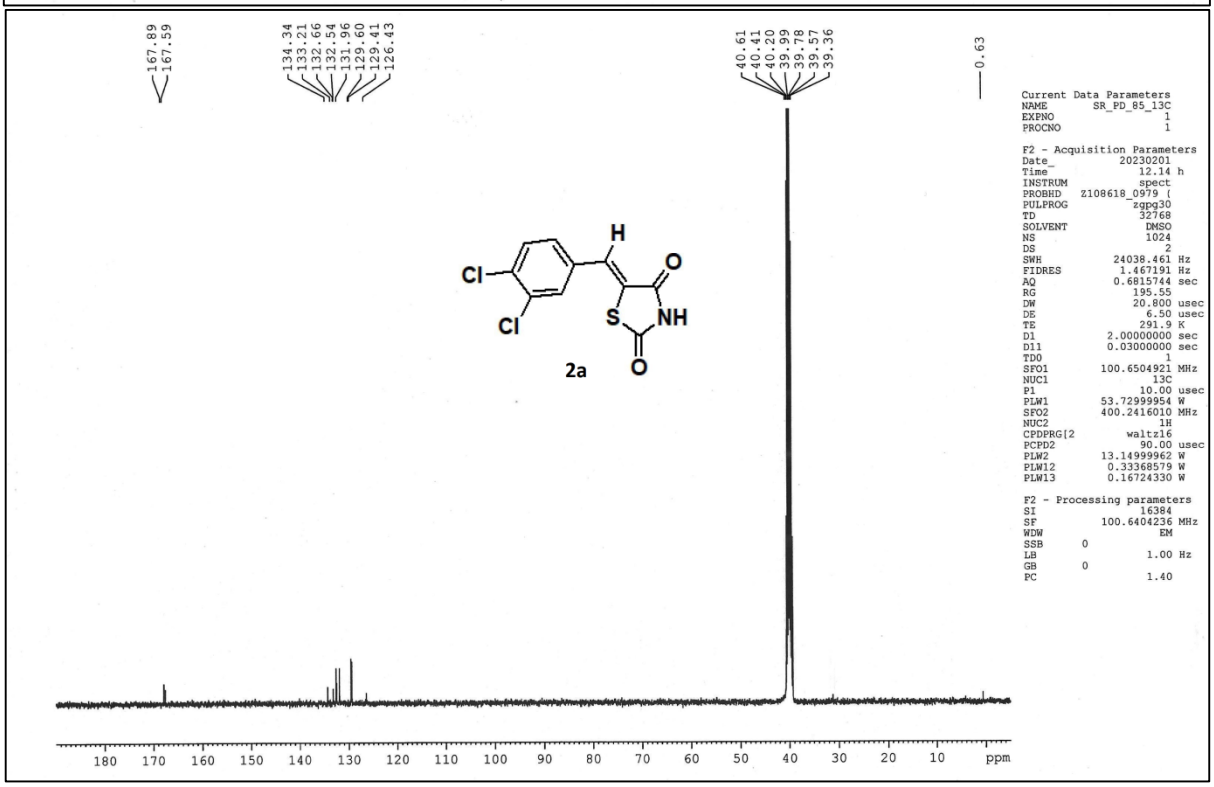


Starting material **1 (or 3, 5, 7)** (1 mmol), $K_2S_2O_8$ (2 mmol), and Eosin Y (0.05 mmol) in DMF were taken in a round bottomed flask and stirred at 50 °C for 4 hours (or until completion) under visible light irradiation by 7W blue LED lamp. The progress of the reaction was monitored by TLC of the reaction mixture. After completion of the reaction the resulting mixture was extracted with EtOAc (3 × 30 mL), and the extracts were combined and dried over Na_2SO_4. After evaporation of solvent, the residue was purified by silica gel column chromatography using hexane/EtOAc as eluent to afford the final product **2** (or **4, 6, 8**).

Spectroscopic Characterization for Final Products:

5-(3, 4-Dichloro-benzylidene)-thiazolidine-2, 4-dione (2a): White solid; m.p. 176 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.76 (1H, brs), 7.90 (s, 1H), 7.81-7.79 (m, 2H), 7.56-7.54 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9, 167.6, 134.3, 133.2, 132.7, 132.5, 132.0, 129.6, 129.4, 126.4, 31.2; HRMS (ESI, M^+) calcd for $C_{10}H_5Cl_2NO_2S$ 272.9418, but found 272.9461.





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User Spectra

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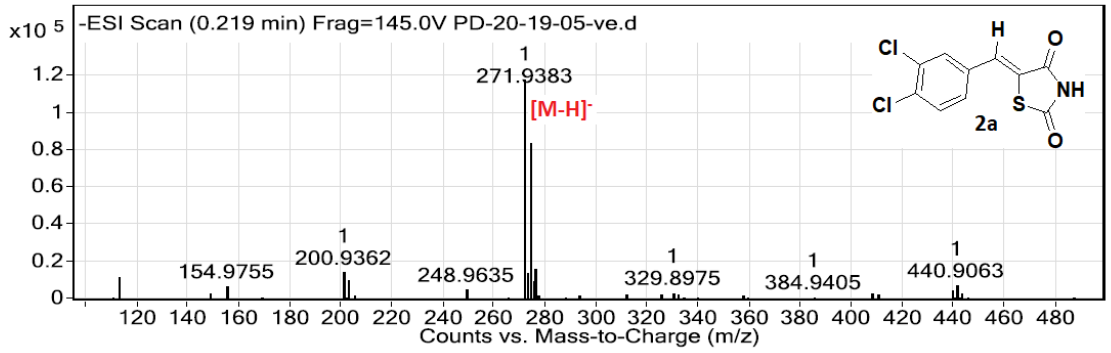
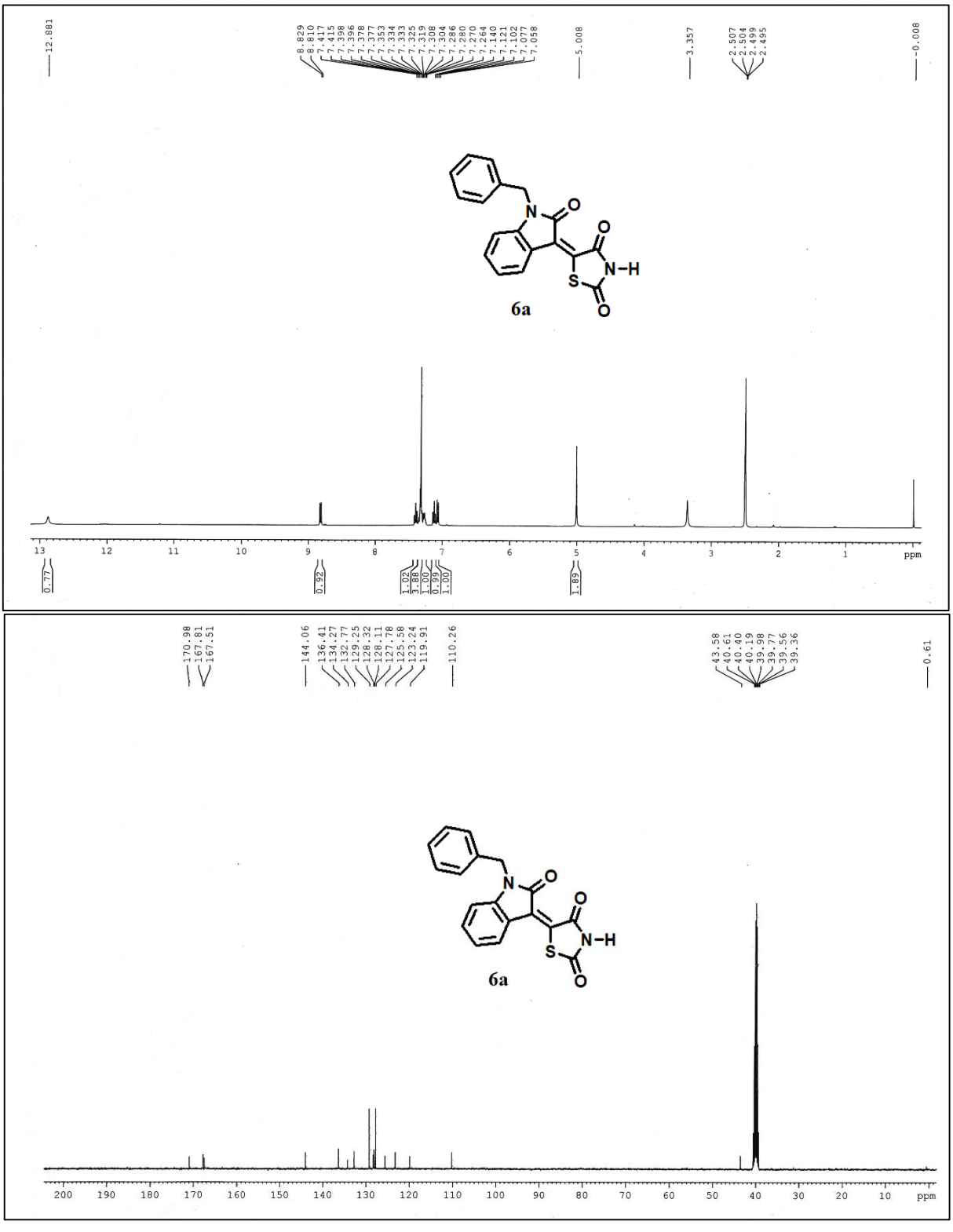
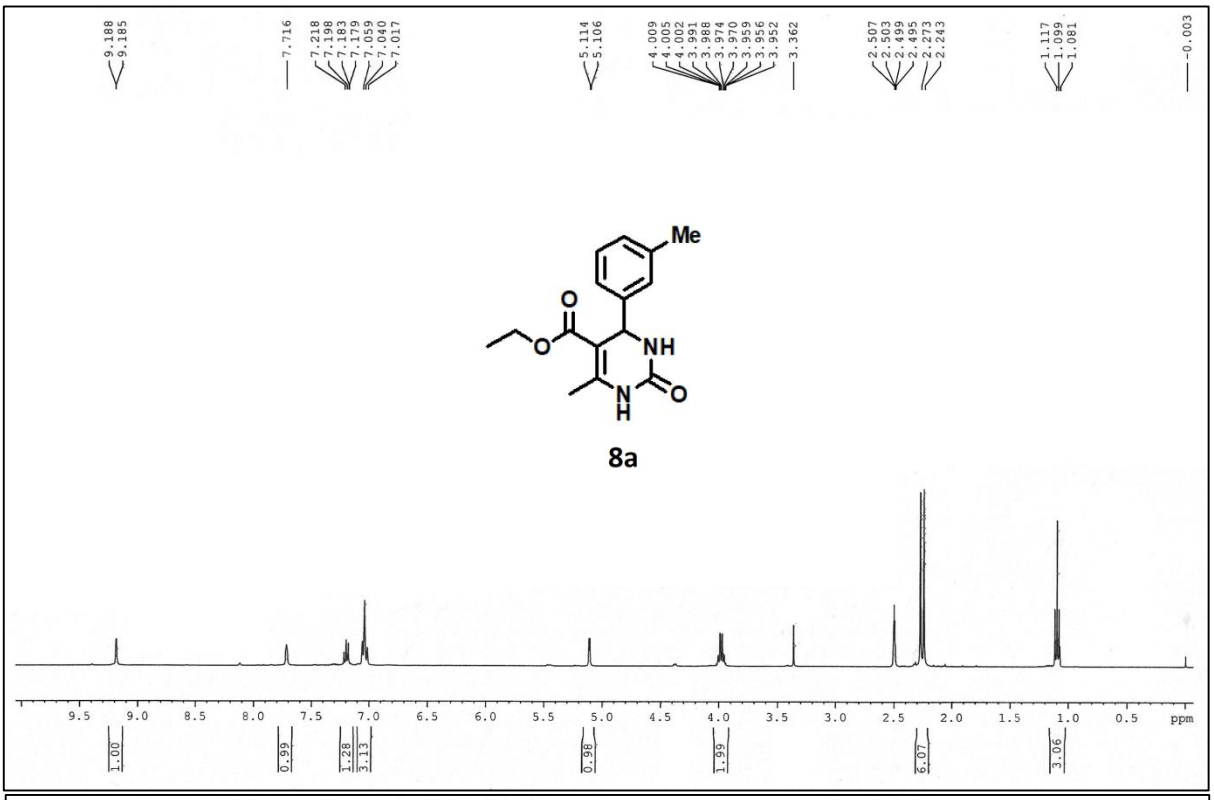
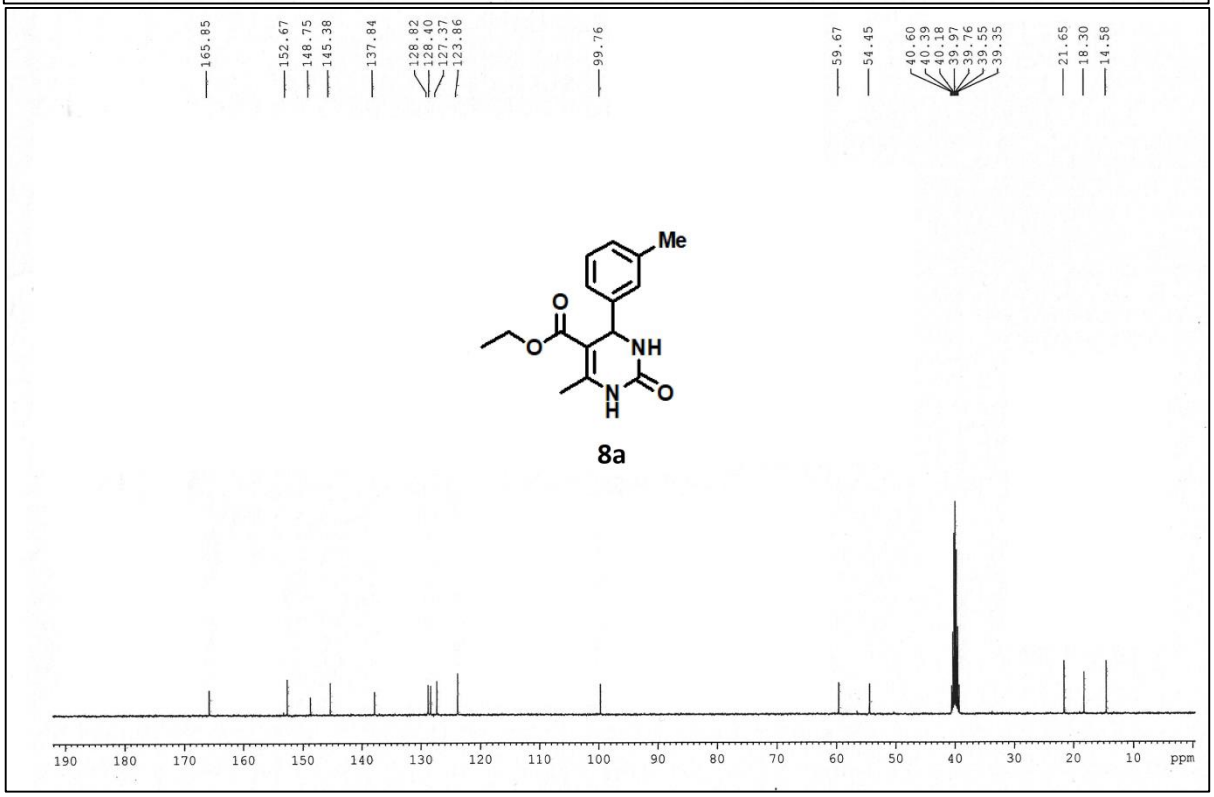


5-(1-Benzyl-2-oxo-1,2-dihydro-indol-3-ylidene)-thiazolidine-2,4-dione (6a): Red solid; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.88 (brs, 1H), 8.82 (d, *J*= 7.6 Hz, 1H), 7.40 (dt, *J*= 0.8 Hz, *J*= 7.6 Hz, 1H), 7.35-7.26 (m, 5H), 7.12 (t, *J*= 7.6 Hz, 1H), 7.07 (d, *J*= 7.6 Hz, 1H), 5.01 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 171.0, 167.8, 167.5, 144.1, 136.4, 134.3, 132.8, 129.3, 128.3, 128.1, 127.8, 125.6, 123.2, 119.9, 110.0, 43.6.



6-Methyl-2-oxo-4-m-tolyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester (8a): White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (brs, 1H), 7.12 (brs, 1H), 7.22-7.18 (m, 1H), 7.06-7.02 (m, 3H), 5.11 (d, J= 3.2 Hz, 1H), 3.98 (qd, J= 1.2 Hz, J= 7.2 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 1.10 (t, J= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 152.7, 148.8, 145.4, 137.8, 128.8, 128.4, 127.4, 123.9, 99.8, 59.7, 54.5, 21.7, 18.3, 14.6.





Conclusion:

The oxidative transformation of thioxo to oxo under extremely mild condition leaving all other easily oxidizable groups untouched is very much alluring in the synthesis of complex bio-active and medicinally important molecules. This is because this particular functional group manipulation is very frequently required during the multistep synthesis of biologically important molecules. Here, we use a very cheap oxidizing agent $K_2S_2O_8$ and exploit the most abundant and green energy source light for thioxo to oxo transformations on various arylidene rhodanines and 3,4-dihydropyrimidine-2(1H)-(thio)ones. The reaction is very efficient, general and highly reproducible. We hope that due to its simplicity, cheapness and environmentally benign nature, the present method will be adopted by synthetic organic chemists for thioxo to oxo in complex molecular systems.

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National Symposium on Frontiers in Chemistry: from Fundamentals to Application (March, 2023): Visible-Light-Mediated Oxidative Desulfurization-Oxygenation in Cyclic Thio-Amide; **Partha Das** and Suman Ray.

Chapter II

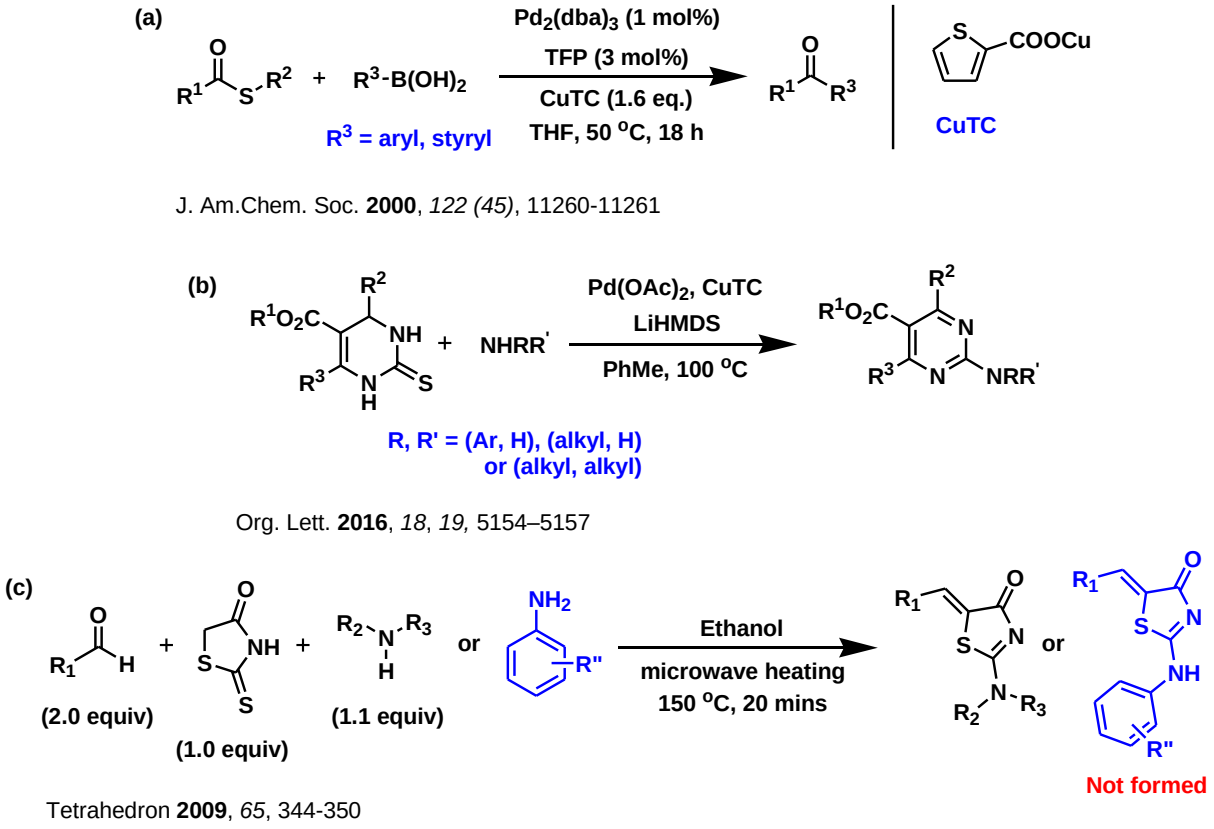
Development of a Metal-Free C-N Cross Coupling Reaction Involving Aliphatic as well as Poorly Nucleophilic Aromatic Amines

Introduction:

Organic chemistry has evolved as an efficient tool to form carbon–carbon and carbon–heteroatom bonds with the advent of transition metal-catalyzed cross-coupling reactions.[1] Many organic compounds which were previously inaccessible can now be synthesized with the help of these reactions like Heck, Negishi, Kumada, Stille, Buchwald-Hartwig, Ullmann and Suzuki.[2] However, all these cross coupling reactions involve an electrophilic partner like aryl-halides, triflates, tosylates or sulfonates which undergo S_NAR reaction with a nucleophilic partner.[3] Though the reactions are certainly very efficient, there is limited scope for the variation of organic halides or triflates etc. as the electrophilic partner.[4] Moreover, the key features of these reactions are the essential involvement base and a catalyst involving transition metals like Pd, Ni, Cu etc. Therefore, reactions with base sensitive functional groups in the substrate poses a great challenge for them.[2a] Another intrinsic problem is the limited stability of organic halides or triflates etc. under basic condition of these reactions.[3] Therefore, in the past decades a great effort had been put into the exploration of new electrophiles as alternate to the traditional organic halides or triflates as well as neutral reaction conditions. In this perspective, organo-sulfur based electrophiles has emerged as an attractive choice of electrophiles for metal catalyzed carbon–carbon and carbon–heteroatom cross coupling reactions because of its ubiquity in biomolecules.[5] However, the use of organo-sulfur as alternative electrophiles in cross coupling reaction received widespread attention only after the pivotal work by Liebeskind and Srogl in 2000 **(scheme 1a)**.[6] In this work they disclosed a mechanistically distinctive Pd catalyzed and Cu(I) carboxylate-mediated coupling between thioesters and boronic acids in non-basic condition leading to ketones; the so called Liebeskind–Srogl cross coupling. Neutral reaction conditions was an intriguing advantage of Liebeskind-Srogl reaction, overcoming the disadvantages associated with the basic condition applied in traditional cross coupling reactions. The success of this reaction boasted its application to other system like thioamide or thiourea containing latent free-thiol group, as revealed by Kappe and others.[7] The nucleophilic partner can be nitrogen, carbon or oxygen centered nucleophiles.[7,8] However, all these reaction must need Pd(0) catalyst and as high as up to 3 equivalents of Cu(I) carboxylate. So, a large amount of metal based waste is generated and thus they lack the green chemistry aspects. So, there is a practical need of for improvement considering the environmental concerns.

Again, among many cross-coupling reactions, C-N cross coupling is key to the synthesis of the systhesis of aromatic amines and also amino(imino)-substituted heterocycles which are ubiquitous in natural products and drug molecules.[9] Moreover, as discussed earlier Liebeskind-Srogl type reaction for C-N coupling offers non-basic condition providing room for base sensitive substrate. Even so, improvements are must needed particularly when using

precious metals like Pd for the production of pharmaceutical ingredients because of contamination of the bio-active molecules with metals and ligands.[10] Furthermore, in order to keep the metal contamination below the permissible level of 10 ppm, the purification costs becomes high and sometimes the tailored design ligands become costlier than the precious metal itself. A significant improvement over the traditional Liebeskind-Srogl type C-N coupling was marked by the Pd-free copper-promoted dehydrosulfurative C–N cross-coupling of thione derivatives with amines as reported by Sohn et al **(scheme 1b)**.[11] Unlike Liebeskind-Srogl type C-N coupling using Pd metal, this protocol as reported by Sohn was certainly a sustainable improvement towards greenness. Despite its success towards the path of sustainable development, it still uses large amount of Cu-based salts and again basic condition by using lithium hexamethyldisilazide (LiHMDS). Moreover, the reaction occurs at 100 °C in DMF under inert condition. In this context, it must be mentioned that Kang and Wan et al. developed completely metal free C−N coupling by phosphonium salts assisted activation of C−OH bonds in cyclic amides.[12] However, the high toxicity of the reagents restricted their use. There are a few other metal free protocols available for desulfitative C-N coupling, which include activation of the C=S bond of thioamide via thio-ether formation reaction, use of high temperature microwave heating, use of strong base etc **(scheme 1c)**.[13]



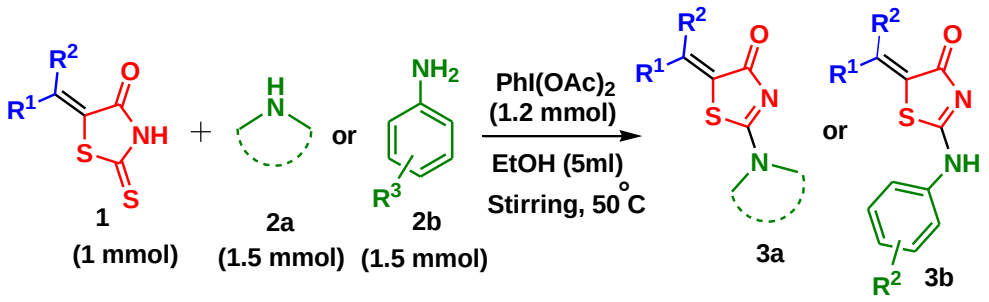
Scheme 1: Previous works

However, all of them exploited the high nucleophilicity of aliphatic primary or secondary amines and none of them were successful with poorly nucleophilic aromatic amine. Moreover, they involve extra step for thio-ether formation, use of base and acids, high temperature, release of H_2S in environment. Therefore, considering the ubiquity of C-N

bonds in natural products and medicinally important compounds, a completely metal free, very mild, environment friendly and cost-effective protocol is very much warranted.

Results and discussions:

Considering the importance of forming C-N bonds during the multistep synthesis of natural products, drugs candidates and other functional molecules containing various sensitive and reactive functional groups, we were interested to develop mild condition for C-N coupling without using strong bases. Moreover, the fact that the precursors of such biologically important molecules frequently contain C–S bonds, inspired us to think about the desulfitative C-N cross coupling reaction under mild conditions so that sensitive functional groups are tolerated. Fortunately, we developed a protocol for selective activation of latent -SH bond using $PhI(OAc)_2$ in presence of –NH and –OH bond; thanks to the unmatched reactivity of hypervalent iodine compounds.[14] Here, we report a $PhI(OAc)_2$ mediated oxidative C-N coupling between 5-alkylidine rhodanine (**1**) and amines (**2**) in EtOH in open air at as low as 50 °C in few hours (**Scheme 2**).



Scheme 2. General Synthetic Scheme showing the formation of C-N bond affording compound **3a** and **3b.**

Most importantly here, poorly nucleophilic aromatic amines reacts equally efficiently as the aliphatic amines. Moreover, here no H_2S is released in the environment, since solid sulphur is precipitated as side product, making this protocol less hazardous. We realized the impact of this metal free desulfitative C-N cross coupling reaction and therefore, interested to find out the optimized reaction condition. We first carried out the reaction at room temperature (30 °C) in ethanol as solvent taking the Knoevenagel condensation product of rhodanine and 3-methyl-benzaldehyde (**1**) (1 equiv.), morpholine (**2**) (1 equiv.) and $PhI(OAc)_2$ (1 equiv.). After 8 hours stirring at room temperature the final product was obtained in 40% yield. The yield increased to 82% in 8 hours when the reaction temperature was elevated at 50 °C. Yield improved further when we varied the amount of morpholine and $PhI(OAc)_2$. 1.5 equivalent of morpholine and 1.2 equivalent of $PhI(OAc)_2$ afforded the best yield of the product (93%). We also tried the reaction in microwave heating condition at 150 °C for 5 minutes, however yield decreased moderately and decomposition of organic compound was observed. Further different solvents were explored to get better yield, however ethanol afforded the cleanest reaction with maximum yield of the product. We also tested the effect on time on the reaction outcome by checking the product yields after 4 and 6 hours. The reaction was incomplete when stopped before 8 hours; also there was no appreciable change in product yield after 8 hours. Therefore, the optimized condition came out as: stirring a mixture of 5-alkylidine

rhodanine (**1**) (1 equivalent), amines (**2**) (1 equivalent) and $PhI(OAc)_2$ (1 equivalent) in EtOH at 50 °C for 8h.

Table 1. Optimization of reaction condition.[a]

Sl. No.	Temp. (°C)	Solvent	$PhI(OAc)_2$ (equiv.)	Amount of amine (2) (equiv.)	Time (h)	Yield[b] (%)
1	30	EtOH	1	1	8	40
2	50	EtOH	1	1	8	82
3	50	EtOH	1.2	1.2	8	86
4	50	EtOH	1.2	1.5	8	93
5[c]	80	EtOH	1.2	1.5	4 min.	83
6	50	EtOH	1.2	1.5	4	50
7	50	EtOH	1.2	1.5	6	70
8	50	EtOH	1.2	1.5	10	94

[a]Reaction condition: 5-Alkylidene-rhodanine (**1**) (1 mmol), $PhI(OAc)_2$ (different amount), amine (**2**) (different amount), stirring at different temperatures for 8 hours. [b]Isolated yields. [c]Microwave heating.

Once, the reaction condition was optimized, it was very crucial to check reproducibility of this proposed protocol. Therefore, we repeated the experiment by taking a number of 5-alkylidene-rhodanine (**1**) compounds which were synthesized by Knoevenagel condensation between rhodanine (**4**) and aldehydes (**5**) or ketones (**6**) and were employed for the above transformation. Aldehydes and ketones containing both electron donating and withdrawing groups, hetero-aromatic aldehydes, purely aliphatic aldehydes and ketones, all underwent this C-N coupling reaction very smoothly with good to excellent yields. Moreover, aldehydes and ketones with substituents at *o*-/*m*-/*p*- positions reacted very smoothly under this present reaction condition. Both cyclic and acyclic aliphatic amines participated in this reaction equally efficiently. The substrate scope for the above mentioned C-N coupling reaction is depicted in **Figure 1**.

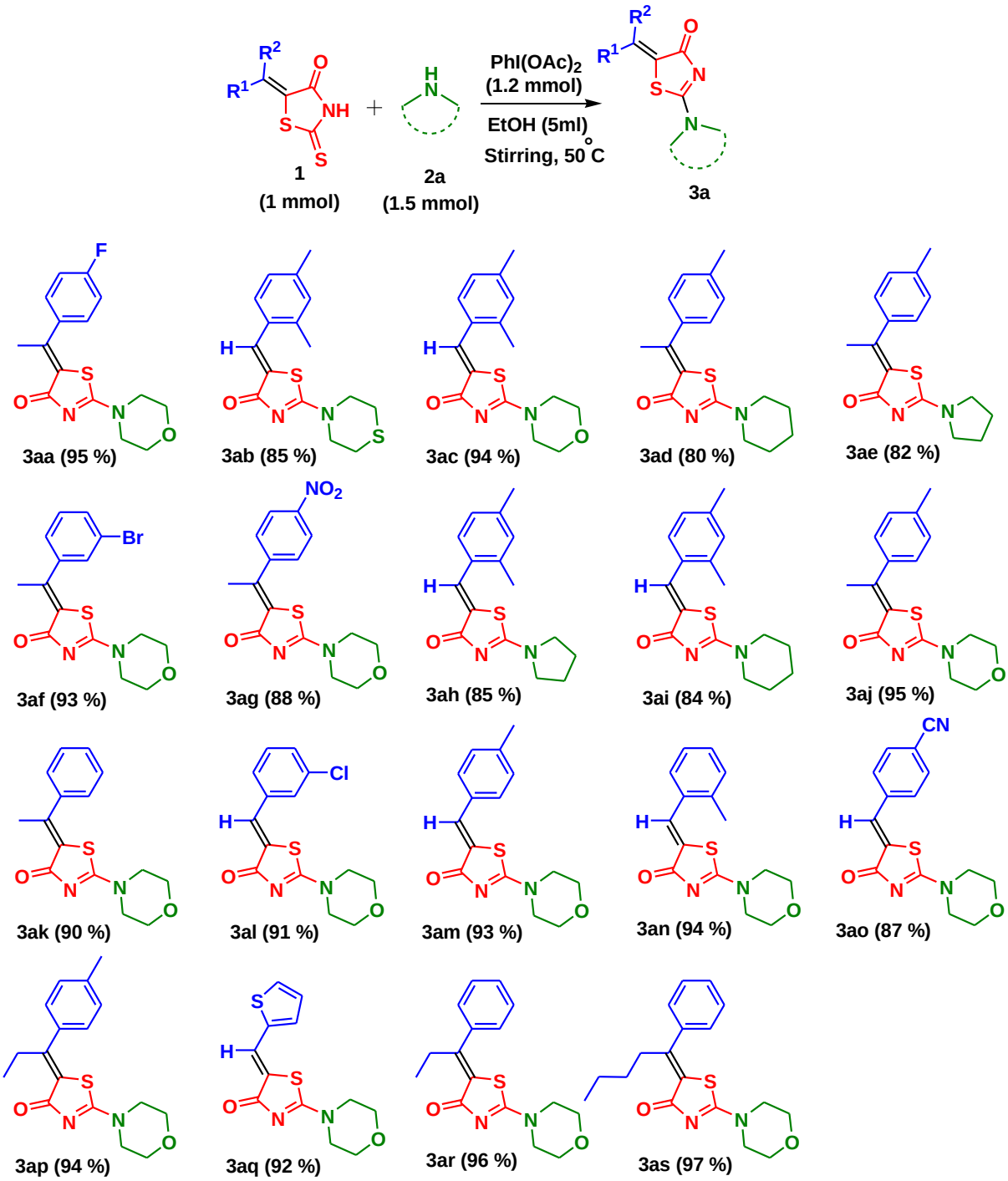


Figure 1: synthesiezed product **3a** by the desulfitative coupling between **1** and **2a**

The most remarkable featutre of this newly developed protocol is the involvement of poorly nucleophilic aromatic amines in the reaction with latent thiol group of rhodanine thioamide in base free condition. Here, the aromatic amines afforded quantitative yield within 10 hours of stirring at 50 °C. Aromatic amines containing both electron donating and withdrawing groups at *m*- and *p*-position afforded the final product (**3b**). However, the *o*-substituted amines could not give the product because of steric interaction of *o*-substituents with rhodanine ring. The products derived from aromatic amines are shown in **Figure 2**.

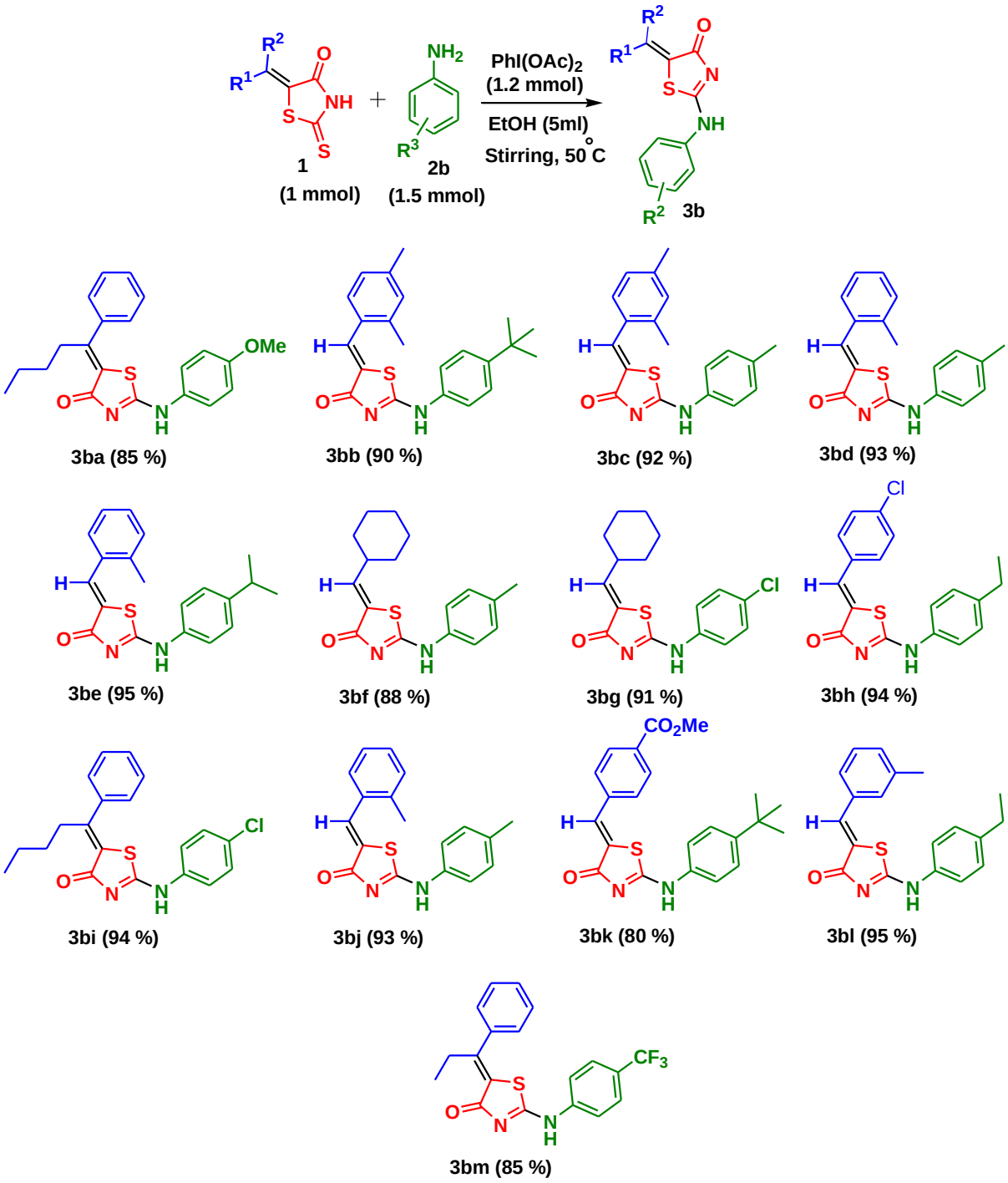
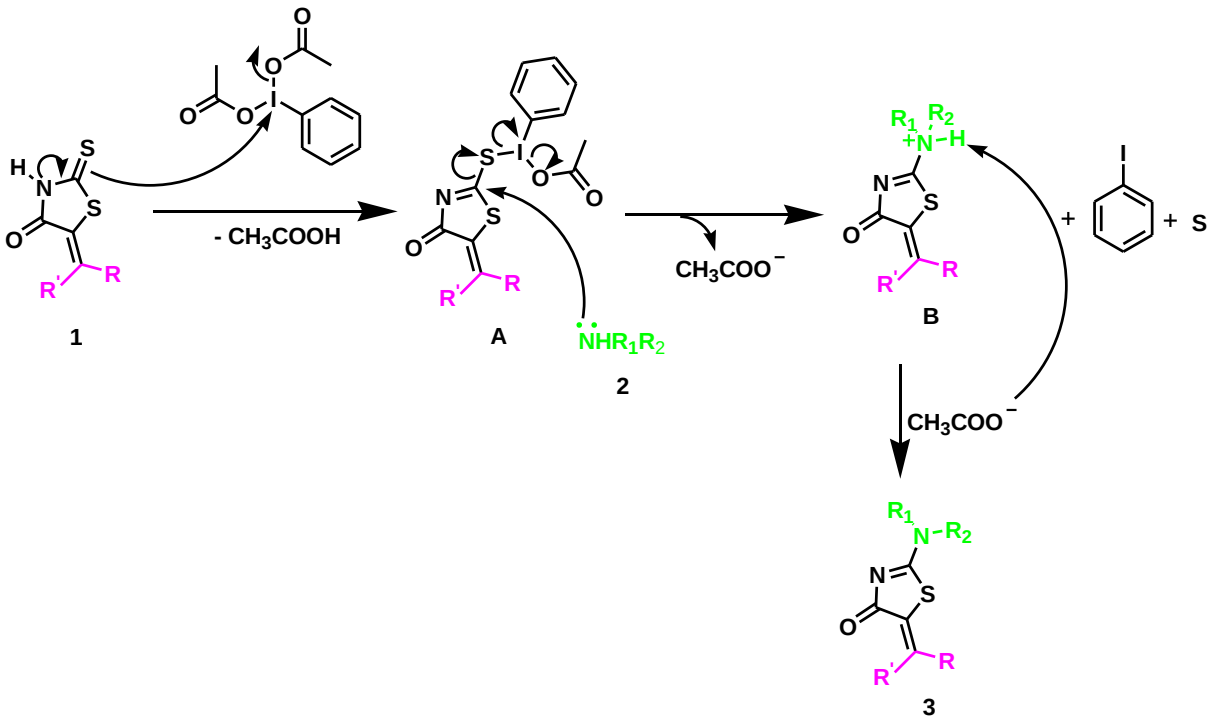


Figure 2: synthesiezed product **3b** by the desulfitative coupling between **1** and **2b**

A probable mechanism for the above mentioned transformation is depicted herein **(scheme 3)**. The thioamide of rhodanine first undergoes tautomerization to give latent thiol group which attacks on the iodine of $PhI(OAc)_2$ and replaces one acetate ion to generate intermediate **(A)**. In this way, thiol is activated and converted to a very good leaving group. Then attack of amine on C-2 of rhodanine ring of **(A)** produces next intermediate **(B)** along with expulsion of PhI and solid elemental sulphur. Intermediate **(B)** after deprotonation by AcO^- affords the final product (**3**).



Scheme 3: Proposed mechanism for the conversion of substrate **1** to **3**

All the compounds can be synthesized in very pure form as evident from the pronon NMR spectra. They were characterized by ^{1}H and ^{13}C NMR, HRMS analyses. Final the unambiguous proof for the obtained molecules was given by X-ray single spectroscopic analysis of compound **(3ar) (Figure 3)**.

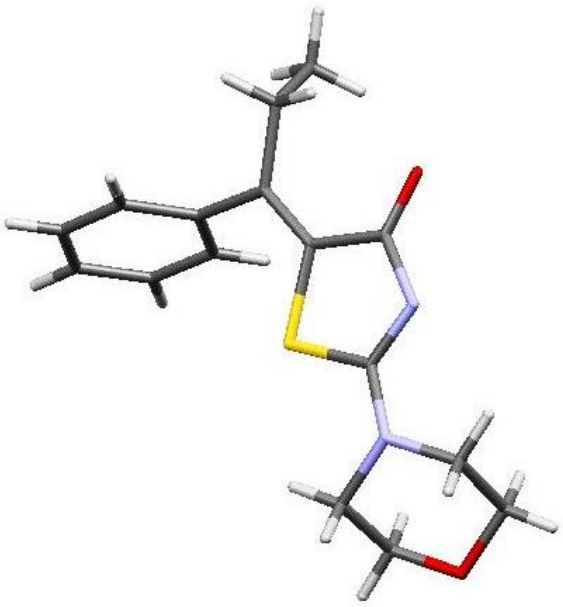
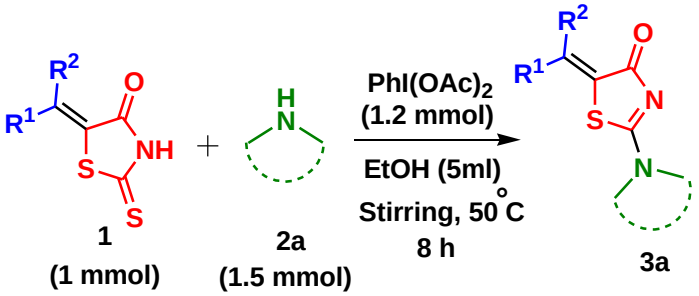


Figure 3: X-ray Single Crystallographic Analysis of **3ar**

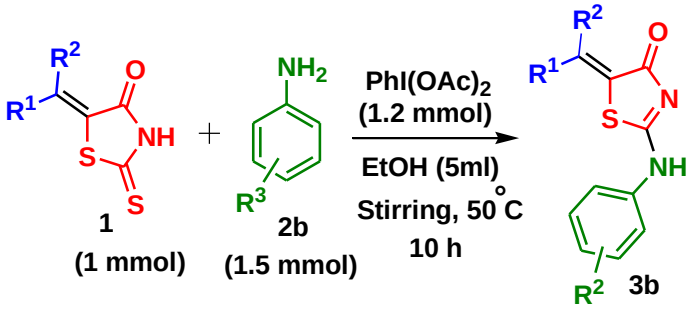
Experimental Section:

Procedure for C-N coupling between 5-alkylidine rhodanines (1) and aliphatic amines (2a) affording (3a):



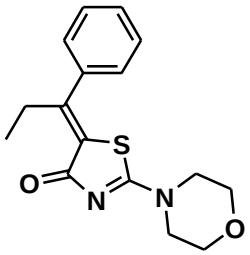
5-alkylidine rhodanine (**1**) (1 equivalent), amines (1.5 equivalent) (**2**) and $PhI(OAc)_2$ (1.2 equivalent) were taken in a 50 ml round bottom flask and about 4 ml ethanol was added to it. Then, the mixture was stirred at 60 ºC for 8 hours. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. Then the product mixture was purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

Procedure for C-N coupling between 5-alkylidine rhodanines (1) and aromatic amines (2b) affording (3b):



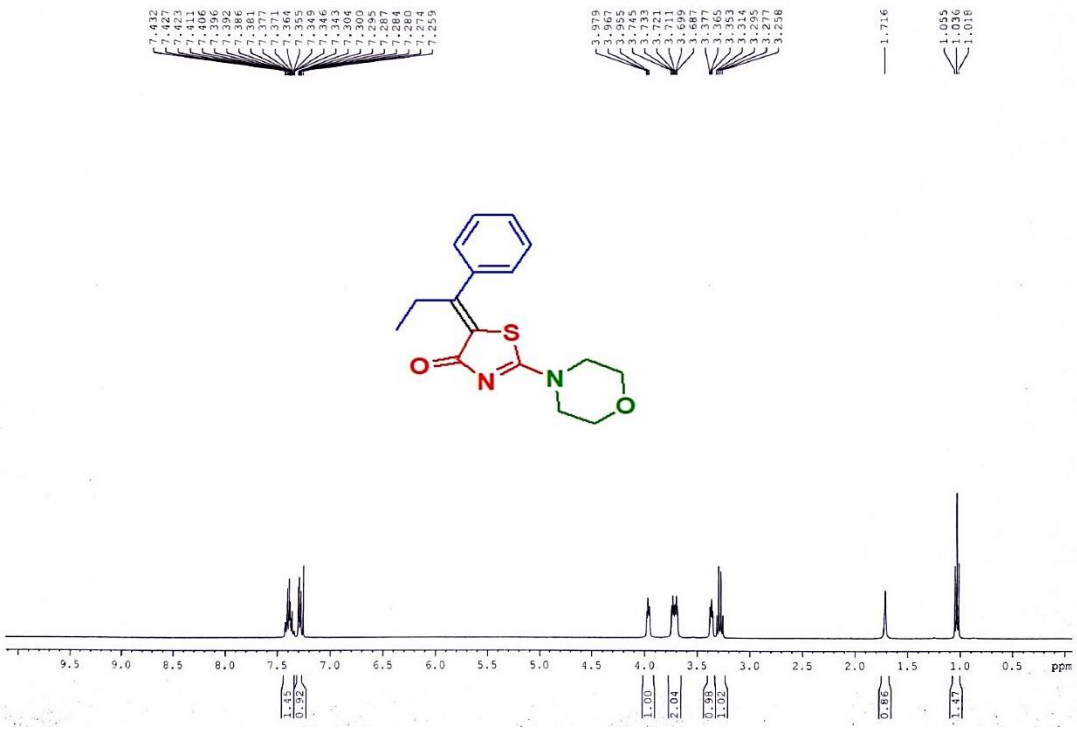
5-alkylidine rhodanine (**1**) (1 equivalent), aromatic amines (1.5 equivalent) (**2**) and $PhI(OAc)_2$ (1.2 equivalent) were taken in a 50 ml round bottom flask and about 4 ml ethanol was added to it. Then, the mixture was stirred at 60 ºC for 10 hours. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. Then the product mixture was purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

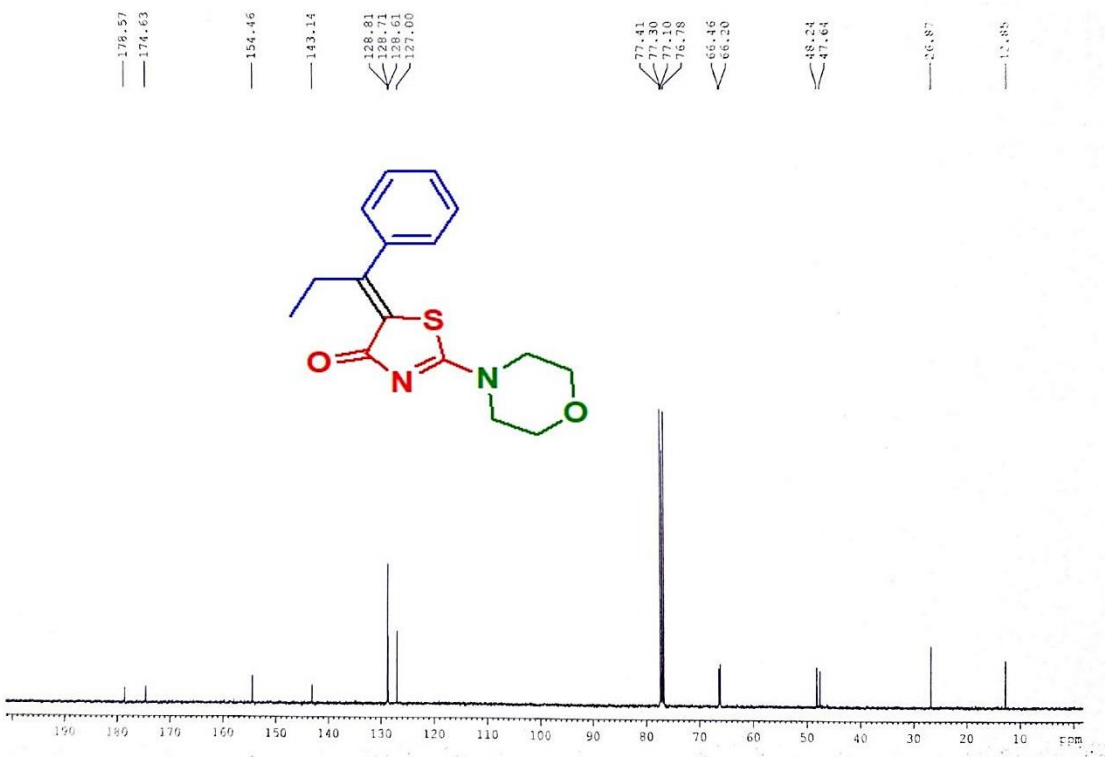
Spectroscopic Characterization for Final Products:

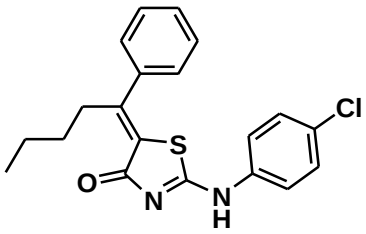


(**3ar)**

2-Morpholin-4-yl-5-(1-phenyl-propylidene)-thiazol-4-one: White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.34 (m, 3H), 7.30-7.27 (m, 2H), 3.97 (t, J= 4.8 Hz, 2H), 3.74-3.69 (m, 4H), 3.36 (t, J= 4.8 Hz, 2H), 3.29 (q, J= 7.6 Hz, J= 14.8 Hz, 2H), 1.04 (t, J= 7.6 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 178.6, 174.6, 154.5, 143.1, 128.8, 128.7, 128.6, 127.0, 66.5, 66.2, 48.2, 47.6, 26.9, 12.8.

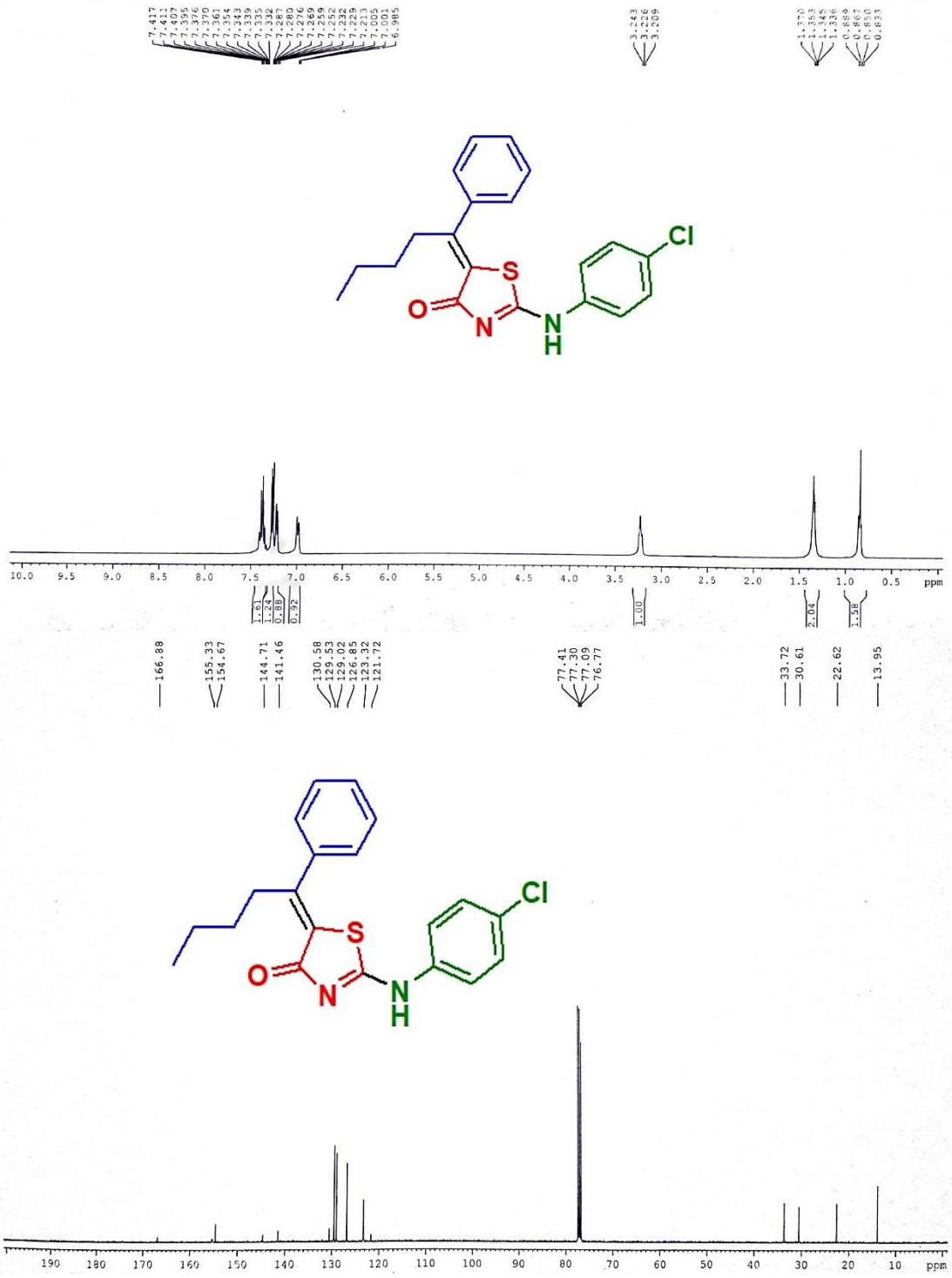


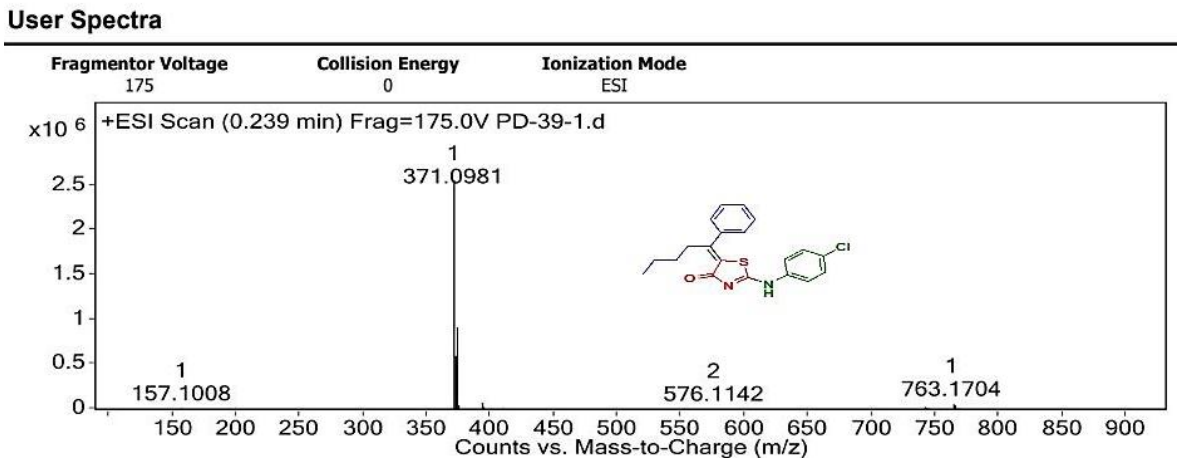




(3bi)

2-(4-Chloro-phenylamino)-5-(1-phenyl-pentylidene)-thiazol-4-one (3bi): White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.33 (m, 3H), 7.29-7.21 (m, 4H), 7.00-6.98 (m, 2H), 3.23 (t, J= 6.8 Hz, 2H), 1.37-1.34 (m, 4H), 0.89-0.83 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 166.9, 155.3, 154.7, 144.7,141.5,130.6,129.5,129.0, 126.8, 123,3, 121.7, 33.7, 30.6, 22.6, 14.0; HRMS (ESI, M^+) calcd for $C_{20}H_{19}ClN_2OS$ 370.0907, but found 370.0981.


7.417
7.411
7.407
7.395
7.376
7.370
7.361
7.354
7.343
7.338
7.335
7.332
7.287
7.280
7.276
7.269
7.259
7.252
7.232
7.229
7.213
7.005
7.001
6.985
3.243
3.226
3.209
1.370
1.353
1.345
1.336
0.869
0.867
0.850
0.833
Cl
S
O
N
N
H
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.61
1.24
0.88
0.92
1.00
2.04
1.58
166.88
155.33
154.67
144.71
141.46
130.58
129.53
129.02
126.85
123.32
121.72
77.41
77.30
77.09
76.77
33.72
30.61
22.62
13.95
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



Conclusion:

Considering the ubiquity of C-S bond in natural products and biomolecules, C-N cross coupling reaction via activation of C-S bond ideally in metal free and mild condition is very much warranted. In this context, this is the first report of completely metal free oxidative desulfitative C-N cross coupling reaction at low temperature involving aliphatic amines as well as poorly nucleophilic aromatic amines at low temperature without requiring microwave heating. The reaction occurs at only 50 °C in excellent yield in nontoxic solvent ethanol without requiring any strong bases. The kind of molecules synthesized here as a consequence of C-N coupling, was never synthesized from aromatic amine in one step metal free reaction. Moreover, unlike previously reported methods where H_2S is released in environment, here solid sulphur is precipitated as by-product. Therefore, the present procedure is eco-friendly as well as economic. Given its simplicity, environment friendliness and economic aspects, the present should receive widespread attention as an alternative to traditional metal catalysed C-N coupling reaction.

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Poster presentation:

P. C. Ray Memorial International Conference on "Contemporary Ideas and Initiatives in Chemical Sciences": A Metal-Free Alternative to Traditional Liebeskind–Srogl Reaction for C-N Cross Coupling Involving Poorly Nucleophilic Aromatic Amines in Non-Basic Condition; **Partha Das** and Suman Ray.

Chapter III

Transition Metal Free Mild Protocol for sp^3 C-H Bond Oxidation Affording Ketones

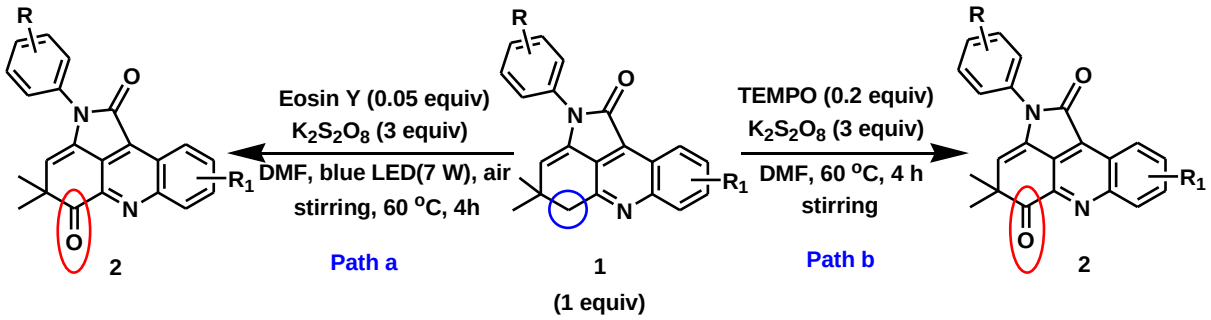
Introduction:

Aryl or heteroaryl ketones are found in many complex bioactive organic molecules like hypericin[1-3], acetosyringone[4-5], oxcarbazepine[6-7], daidzein[8-9], sitaxentan[10-11]etc. Oxidation of methylene group of the alkyl substitution on aromatic or heteroaromatic ring is an excellent strategy to form carbonyl derivatives. Among the many synthetic procedures devloped for the preparation of aromatic ketones, methylene oxidation stands out as a simple and attractive approach in last few decades. Many reagents like $KMnO_4$, iodine(V) species, ^tBuOOH, m-CPBA, H_2O_2, NHPI etc., have been found useful for the benzylic methylene oxidation or sp^3 C-H oxidation to form aromatic ketones. Although most of these methods give good yields and also very selective, stoichiometric amounts[12-13] of oxidizing agents are required which are relatively harmful or unsafe. These reagents also leave harmful toxic waste making these methodologies not so environment benign. In the last few decades, transition metal catalysed (Cu(I), Cu(II), Co(II), Rh(II), Fe(II), Fe(III), Pd(II), Mg(II), Mn(II) or Ni(II) complexes)[14-23] benzylic oxidation methods has been emerged as an interesting and attractive synthetic protocols for complex and bio active aromatic ketone molecules. All of these proceses gives high product yield. But most of the metal catalysts are toxic and are of high cost. Beside this, these reagents leaves toxic and harmful metallo waste. These inherent problems are yet to be resolved.

Therefore, we herein report two different general and mild, transition metal free oxidative pathway for the oxidation of the α-methylene carbon of 2-alkyl group of pyridine derivatives affording corresponding ketones.

Results and disscussion:

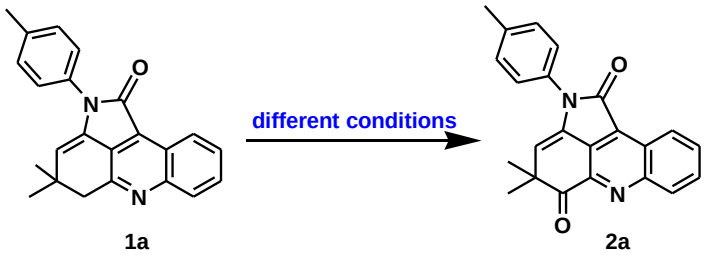
In this present study, we initially performed the oxidation of methylene carbon in substrate **1** under photocatalytic condition using Eosin Y as photocatalyst, $K_2S_2O_8$ as terminal oxidant under blue light irradiation (**Scheme 1, path a**) affording corresponding ketones (**2**). Next, during the optimization we realized that the reaction could be carried out using TEMPO as catalyst with same terminal oxidant $K_2S_2O_8$ without using any light and photocatalyst (**Scheme 1, path b**). In both methods, the product yield was excellent. This reaction condition shows very high functional group tollerance in both amines and isatins.



Scheme 1: Oxidation of the α-methylene carbon of 2-alkyl group of pyridine derivatives affording corresponding ketones.

To increase the yield and to find out even mild condition for this protocol, we were interested. In order to optimize the reaction conditions, we undertook a lot of background studies and the results are summarized in Table 1. For the purpose 4,4-Dimethyl-2-p-tolyl-4,5-dihydro-2H-pyrrolo[2,3,4-kl]acridin-1-one **(1a)** which was obtained by condensation between demidone and p-toluidine followed by treating the condensation product with isatin, was chosen as a model substrate to afford **2a**.

Table 1: Optimization of reaction condition



Entry	Catalyst	Oxidant	Solvents	Aerial Atmp.	Temp. (°C)	Light	Yield (%)	Time (h)
1	Eosin Y	$K_2S_2O_8$ (2 eqv)	DMF	Ar	50	Blue LED	80	4
2	Eosin Y	-	DMF	O_2	50	Blue LED	30	4
3	-	$K_2S_2O_8$ (2 eqv)	DMF	Open air	50	-	50	4
4	Eosin Y	$PhI(OAc)_2$	DMF	Ar	50	Blue LED	20	4
5	Eosin Y	TEMPO	DMF	Ar	50	Blue LED	Trace	4
6	-	TEMPO	DMF	Ar	50	-	Trace	4
7	Eosin Y	TEMPO	DMF	Open air	50	Blue LED	35	4
8	Eosin Y	$K_2S_2O_8$(2 eqv) + TEMPO (1.2 eqv)	DMF	Ar	50	Blue LED	90-95	4

9	-	$K_2S_2O_8$(2 eqv) + TEMPO (2 eqv)	DMF	Open air	50	-	90-95	2
10	-	TEMPO	DMF	Open air	50		Trace	4
11	-	$K_2S_2O_8$ (1 eqv)	DMF	Open air	50	-	40	2
12	-	$K_2S_2O_8$(2 eqv) + TEMPO (2 eqv)	EtOH	Open air	50	-	90-95	4
13	Eosin Y	t-BuOOH	DMF	Ar	50	Blue LED	-	4
14	-	t-BuOOH (2 eqv) + TEMPO (2 eqv)	DMF	Open air	50	-	Trace	4
15	**-**	**$K_2S_2O_8$(2 eqv) + TEMPO (0.2 eqv)**	**DMF**	**Open air**	**50**	**-**	**95**	**3**
16	-	$K_2S_2O_8$(0.2 eqv) + TEMPO (2 eqv)	DMF	Open air	50	-	80-85	3
17	-	$PhI(OAc)_2$ (2 eqv) + TEMPO (2 eqv)	DMF	Open air	50	-	60-70	3
18	-	$K_2S_2O_8$(2 eqv) + TEMPO (0.2 eqv)	Toluene	Open air	50	-	No reaction	
19	**Eosin Y**	**$K_2S_2O_8$ (2 eqv)**	**DMF**	**Open air**	**50**	**Blue LED**	**90-95**	**4**
20	-	$K_2S_2O_8$(1 eqv) + TEMPO (0.2 eqv)	DMF	Open air	50	-	40-45	3
21	Eosin Y	$K_2S_2O_8$ (2 eqv)	AcCN	Ar	50	Blue LED	No reaction	4
22	Eosin Y	$K_2S_2O_8$ (2 eqv)	AcCN (4 ml) + 4-5 drops water	Ar	50	Blue LED	40	4
23	Eosin Y	$K_2S_2O_8$ (2 eqv)	EtOH	Open air	50	Blue LED	No reaction	4

24	-	$K_2S_2O_8$(0.2 eqv) + TEMPO (1 eqv)	DMF	Open air	50	-	60-70	4
25	-	$K_2S_2O_8$(2 eqv) + TEMPO (0.2 eqv)	DMF	Open air	r.t.	-	60-70	4
26	Eosin Y	$K_2S_2O_8$ (2 eqv)	DMF	Open air	r.t.	Blue LED	5-10	4

For the initial studies DMF was chosen a trial solvent because of good solubility of the highly polar substrates. The reaction was going well when we had used $K_2S_2O_8$ as terminal oxidant and the reaction was catalysed by eosin Y in innert atmosphere under blue LED irradiation for 4 h at 60 °C **(entry 1)**. But we had wanted to enhance the product yield even more and make the condition more mild. However, in presence of Eosin Y as photocatalyst under blue light without any oxidant, only trace amount of the product was obtained in O_2 atmosphere **(entries 2)**. After repeating **entry 1** condition without eosin Y, we had found only a trace amount of product (entry 3). There after, we had changed the terminal oxidant keeping the other conditions same, but combination of $K_2S_2O_8$ with TEMPO had emerged as best one **(entry 8)**. When we had changed the solvent and used solvents like AcCN, tolune **(entry 18,21)** no reaction was taken place. But after addition of few drops of water into AcCN **(entry 22)**, the product yield was found to near about 40 %. This results indicates the requirement of water in the medium. From the controled experiments, it was also establised that 2 equiv. or more $K_2S_2O_8$ was required. After varrying aerial condition, catalytic condition, solvents, temperature, light etc., we had found two different optimized conditions **(entry 15 and entry 19) (Table 1).**

Once the optimized condition was obtained, in order to check the reproducibility of our newly developed protocol, a number of different non oxidized compounds were synthesized by the condensation between demidone and amines followed by treating the product with isatin or substituted isatins and the non-oxidized products were employed for the said transformations to generate corresponding oxidized product **(figure 1)**.

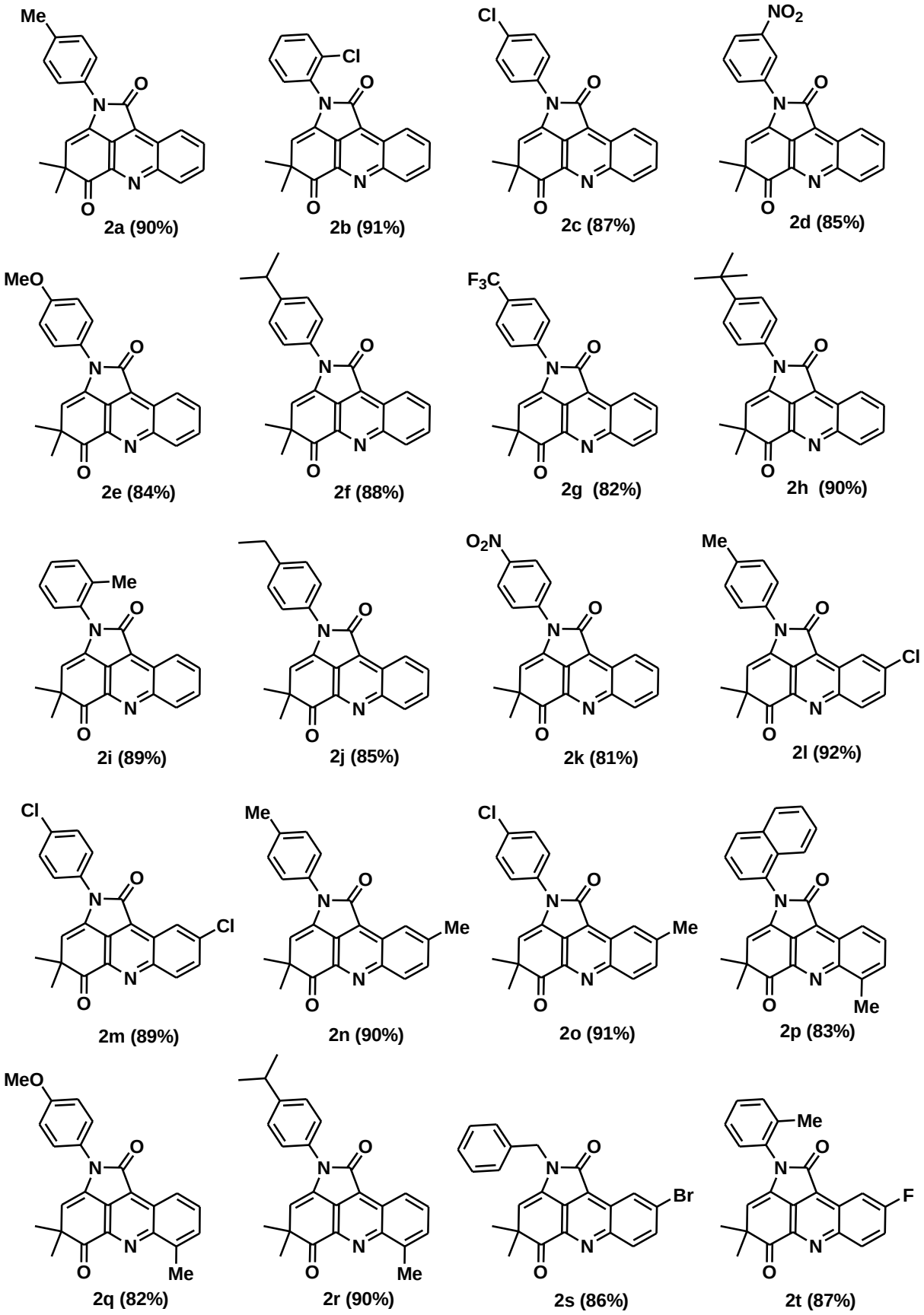
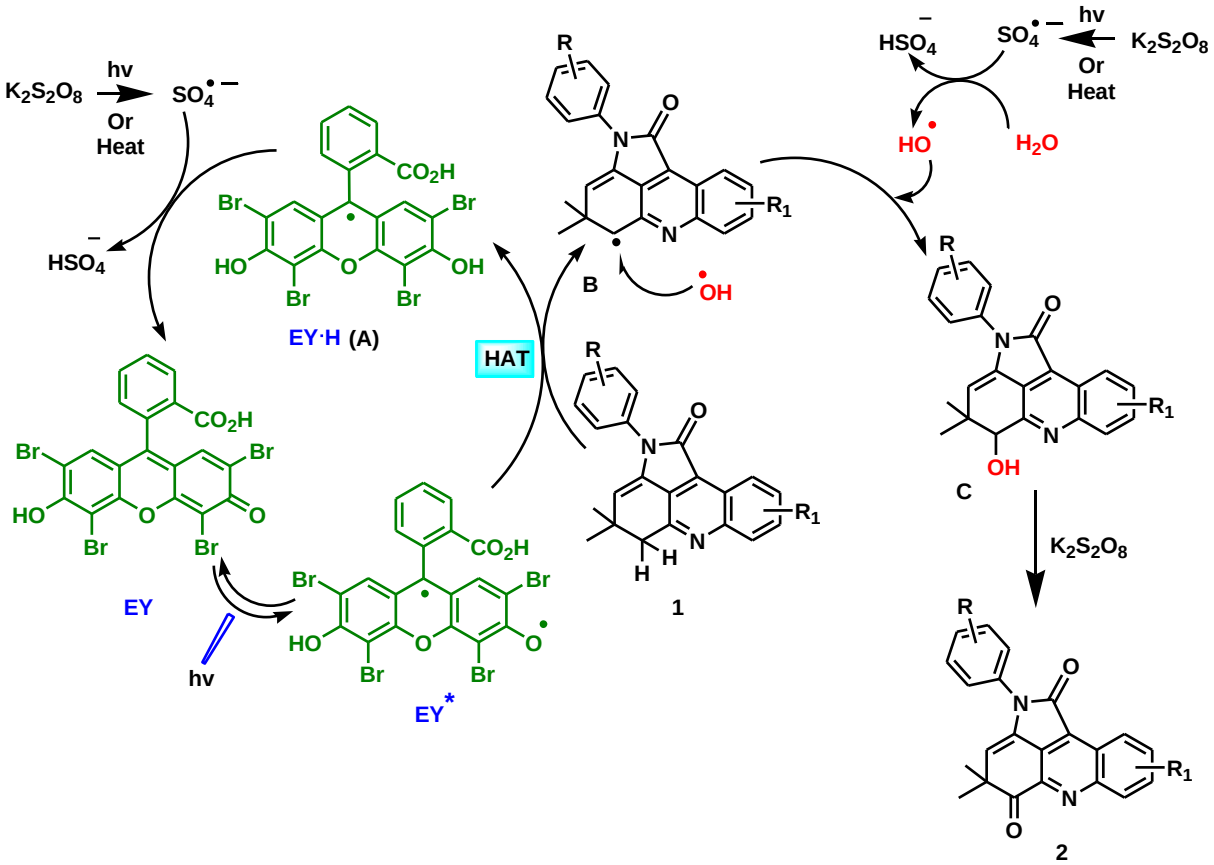


Figure 1: Synthesized oxidized products **2** from substrate **1**

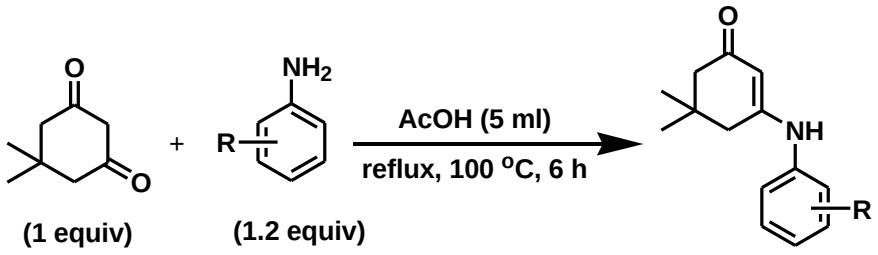
Now, based on the optimization studies and literature survey, we herein propose the following reaction mechanism **(Scheme 2).** From the literature studies, we come to know that on heating or light exposition, decomposition of $K_2S_2O_8$ takes place to generate a sulfate radical anion ($SO_4^{\cdot -}$)[38] and at the same time the photocatalyst Eosin Y (EY) is activated to give excited state eosin (EY*) on irradiation with blue LED. The excited state eosin Y abstract hydrogen from non-oxidized compound **(1)** and produces the radical intermediates **A** and **B** from eosin and substrate **(1)** respectively. The intermediate **A** undergoes oxidation by $SO_4^{\cdot -}$ and back into the ground state Eosin Y. Again, during optimization of the reaction condition it is established that three equivalents of $K_2S_2O_8$ are required and also the presence of water is essential for this reaction. Here the second equivalent of $K_2S_2O_8$ undergoes decomposition and produces another sulfate radical anion in the similar way. This sulfate radical anion accepts a hydrogen radical ($H^{\cdot}$) from water to produce the hydroxyl radical ($OH^{\cdot}$). Now, the intermediate **B** undergoes interaction with hydroxyl radical to form intermediate **(C)**. Finally the intermediate **(C)** oxidized into the final product **(2)** by remaining $K_2S_2O_8$ and TEMPO.



Scheme 2: Proposed reaction mechanism for the conversion of substrate**1** to oxidized product **2**

Experimental Section:

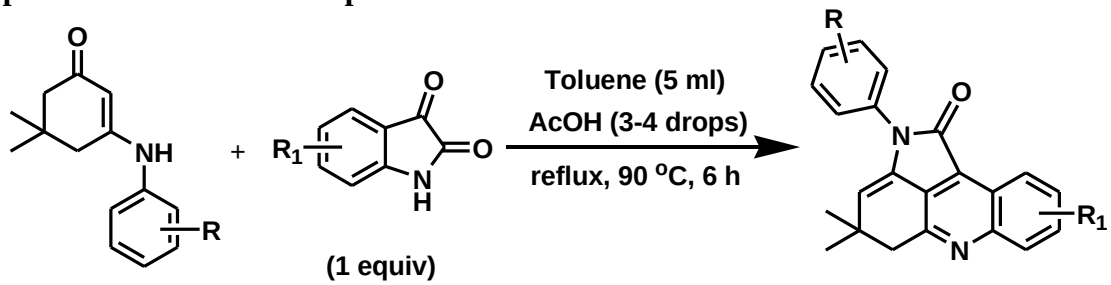
Preparation of Enaminoketone by the condensation between demidone and amine:



Enaminoketone

1 equiv. demidone and 1.2 equiv. amine were taken into a 50 ml round bottom flask, 5 ml acetic acid was added to it. Then the mixture was refluxed for 6 h at 100 ºC in an oil bath. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. Then the product mixture was purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

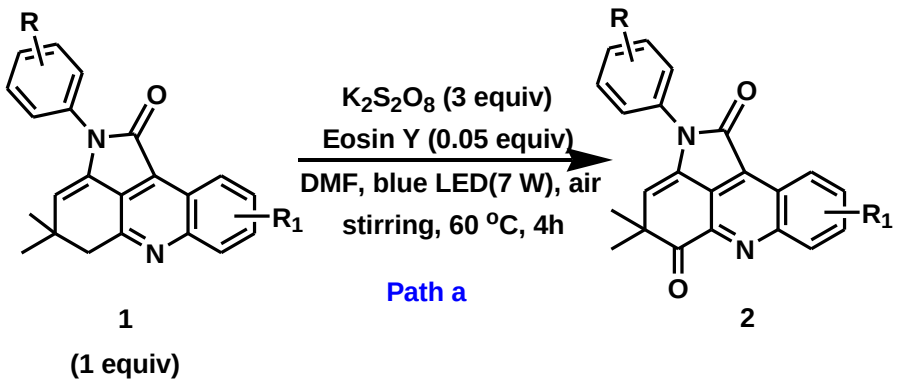
Preparation of non oxidized product 1:



Non oxidised product

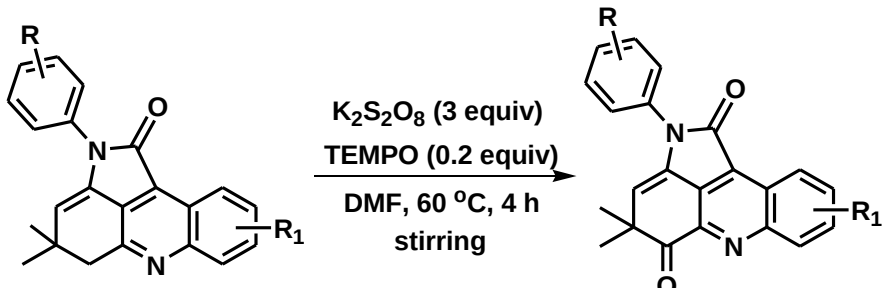
1 equiv. enaminoketone and 1 equiv. isatin were taken into a 50 ml round bottom flask, 5 ml toluene was added to it and acetic acid was taken in catalytic amount. Then the mixture was refluxed for 6 h at 90 ºC in an oil bath. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. Then the product mixture was purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

Preparation of oxidized product by pathway a:



1 equiv. non oxidized product (5), 3 equiv. $K_2S_2O_8$ and 0.05 equiv. eosin Y were taken into a 50 ml round bottom flask, 5 ml DMF was added to it. Then the mixture was stirred for 4 h at 60 ºC in a water bath under blue LED excitation. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. The reaction mixture was worked up using ethyl acetate and water in a seperating funnel. After extraction, the solvent was removed under reduced pressure by rotatory evaporator and purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

Preparation of oxidized product by pathway b:



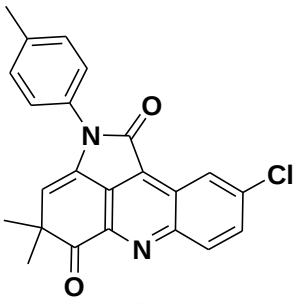
1

(1 equiv)

2

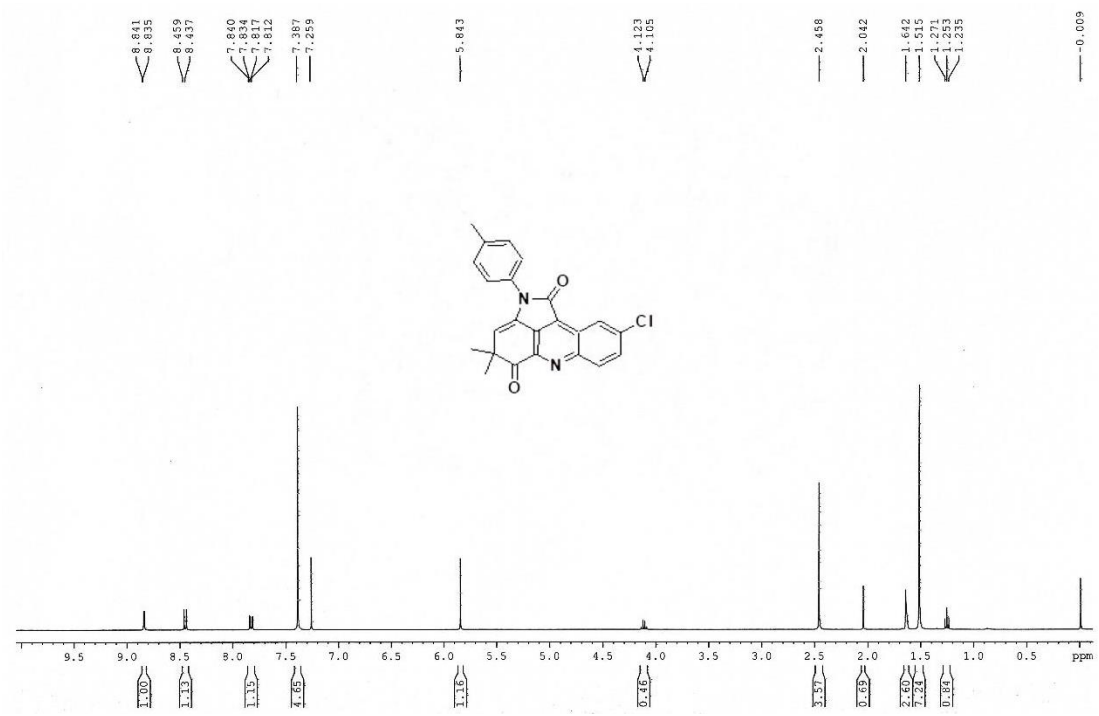
1 equiv. non oxidized product (5), 3 equiv. $K_2S_2O_8$ and 0.2 equiv. TEMPO were taken into a 50 ml round bottom flask, 5 ml DMF was added to it. Then the mixture was stirred for 4 h at 60 ºC in a water bath. The progress of reaction was monitored by TLC using Hexane/EtOAc eluent. The reaction mixture was worked up using ethyl acetate and water in a seperating funnel. After extraction, the solvent was removed under reduced pressure by rotatory evaporator and purified by column chromatography on silica gel gave using Hexane/EtOAc as eluent.

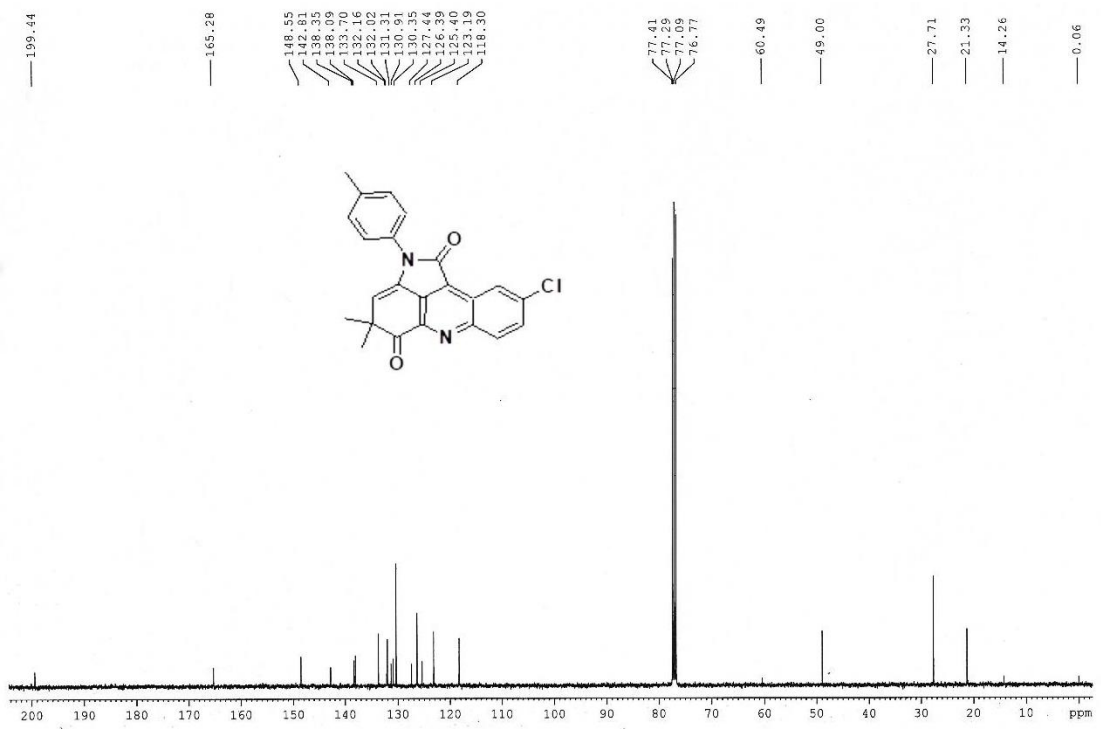
Spectroscopic Characterization for Final Product (7a):

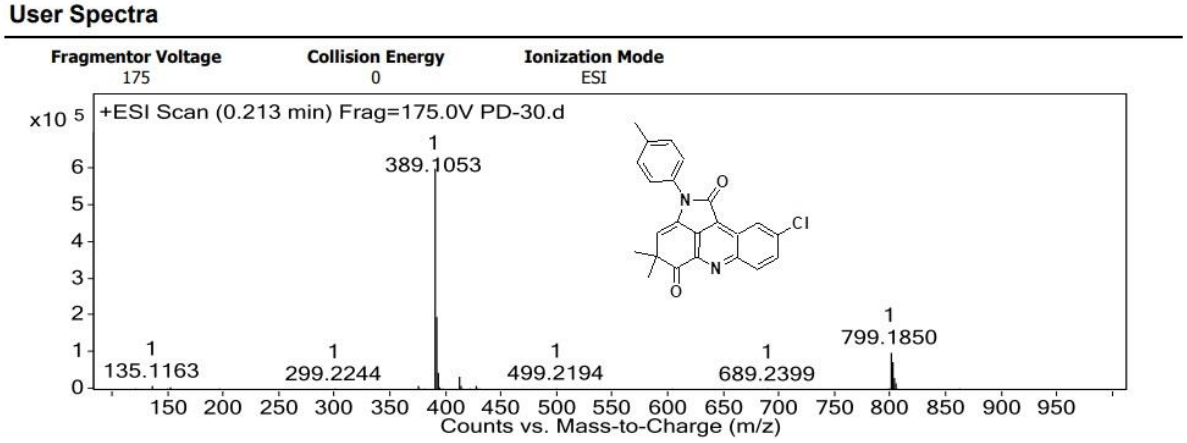


2l

9-Chloro-4,4-dimethyl-2-p-tolyl-2,4-dihydro-pyrrolo[2,3,4-kl]acridine-1,5-dione (2l): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.84 (d, J= 2.4 Hz, 1H), 8.45 (d, J= 8.8 Hz, 1H), 7.82 (dd, J= 2.4 Hz, J= 9 Hz, 1H), 7.39 (s, 3H), 5.84 (s, 1H), 2.46 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 199.4, 165.3, 148.6, 142.8, 138.4, 138.1, 133.7, 132.2, 132.0, 131.3, 130.9, 130.4, 127.4, 126.4, 125.4, 123.2, 118.3, 60.5, 49.0, 27.7, 21.3, 14.3; HRMS (ESI, M+ H) calcd for $C_{23}H_{17}ClN_2O_2$ 388.0979, but found 388.1053







Conclusion:

sp^3 C-H oxidation at benzylic possition into corresponding ketones under extremely mild condition leaving all other easily oxidizable groups untouched is very much alluring in the synthesis of complex organic molecules, bio-active and medicinally important molecules. This synthetic methods are frequently used for the synthesis of complex or bio active organic molecules containing other sensitive oxidisable parts within the molecules.here we report two different mild, ecofriendly methods for the sp^3 C-H oxidation to from corresponding ketones with other sensitive easily oxidisable methylene part unchanged. The reaction is very efficient, general and highly reproducible. We hope that due to its simplicity, cheapness and environmentally benign nature, our devloped methods will be adopted by synthetic organic chemists whenever sp^3 C-H bond oxidation or benzylic oxidation will be required for the synthesis of complex bio active molecules or other organic molecules.

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